



US 20250255941A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2025/0255941 A1
(43) Pub. Date: Aug. 14, 2025

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

A61K 47/64 (2017.01)
A61K 47/66 (2017.01)
A61P 17/14 (2006.01)
A61Q 7/00 (2006.01)

(71) Applicant: BPMED CO., LTD., Seoul (KR)

(52) U.S. Cl.
CPC *A61K 38/4893* (2013.01); *A61K 8/66* (2013.01); *A61K 47/64* (2017.08); *A61K 47/66* (2017.08); *A61P 17/14* (2018.01); *A61Q 7/00* (2013.01); *C12Y 304/24069* (2013.01)

(21) Appl. No.: 18/703,591

(57) ABSTRACT

(22) PCT Filed: Jul. 6, 2022

(86) PCT No.: PCT/KR2022/009761

§ 371 (c)(1),
(2) Date: Apr. 22, 2024

(30) Foreign Application Priority Data

Oct. 22, 2021 (KR) 10-2021-0141684
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.

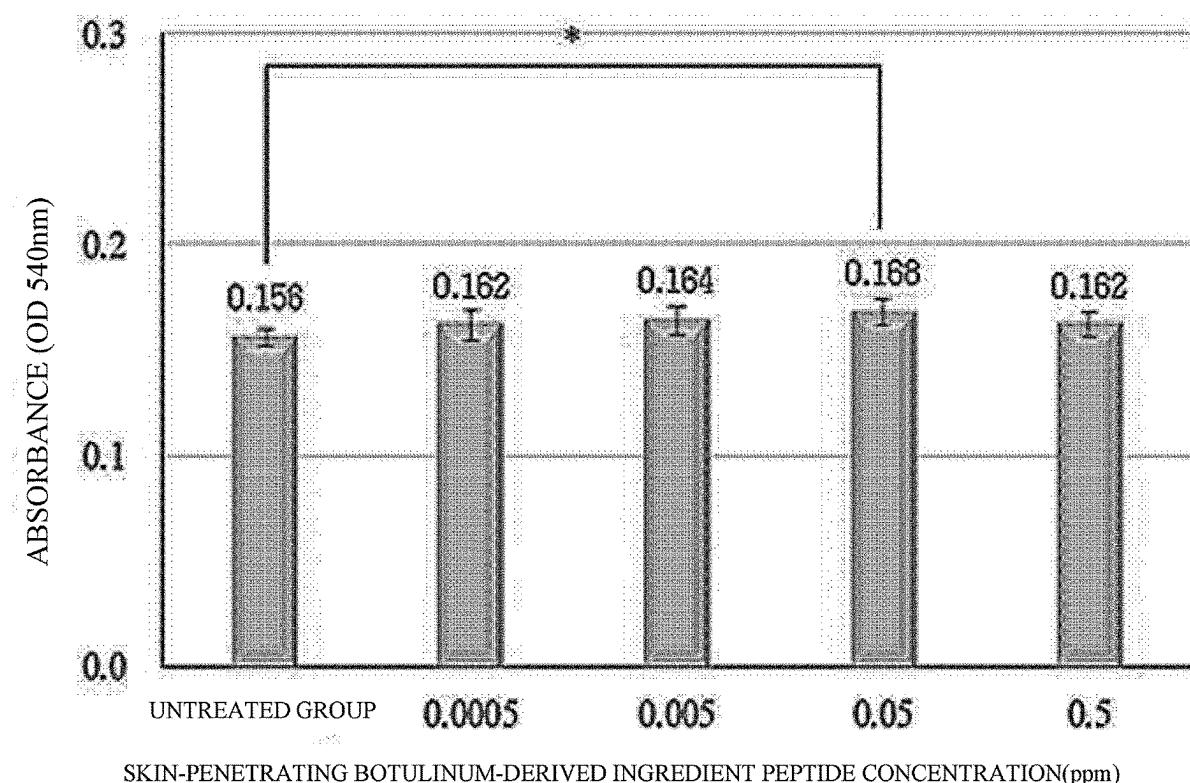
A61K 38/48 (2006.01)
A61K 8/66 (2006.01)

FIG. 1

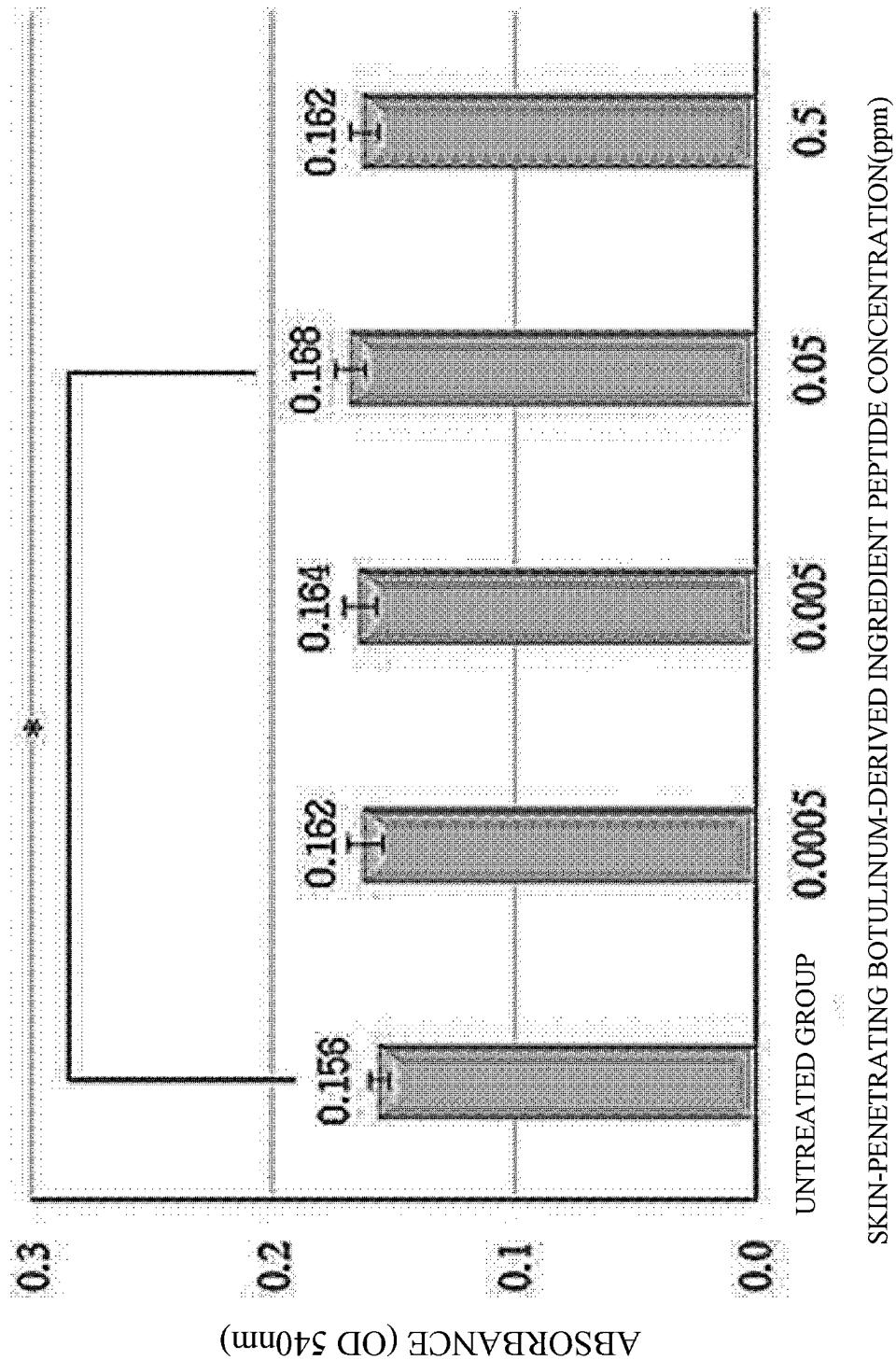


FIG. 2

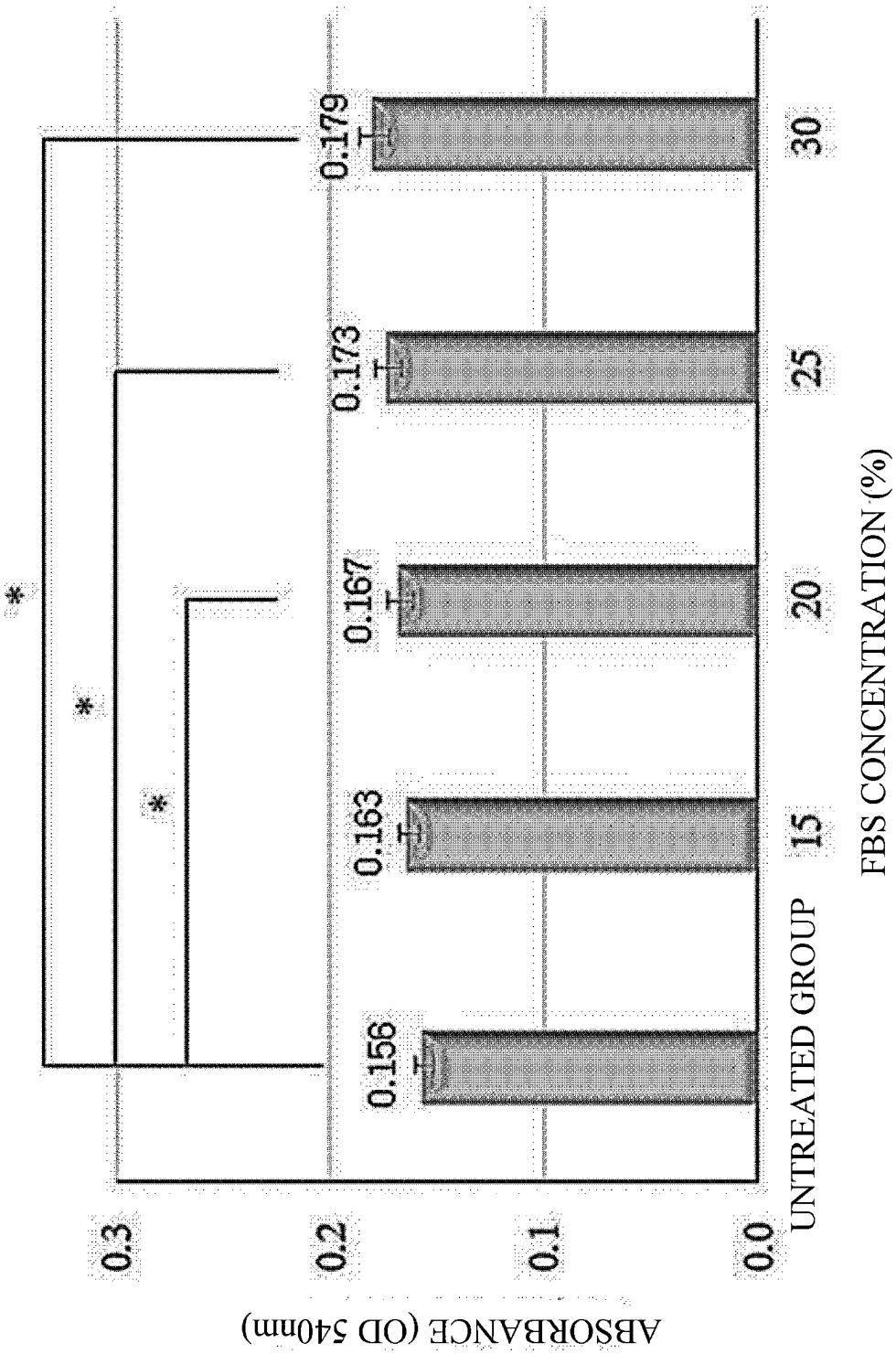


FIG. 3

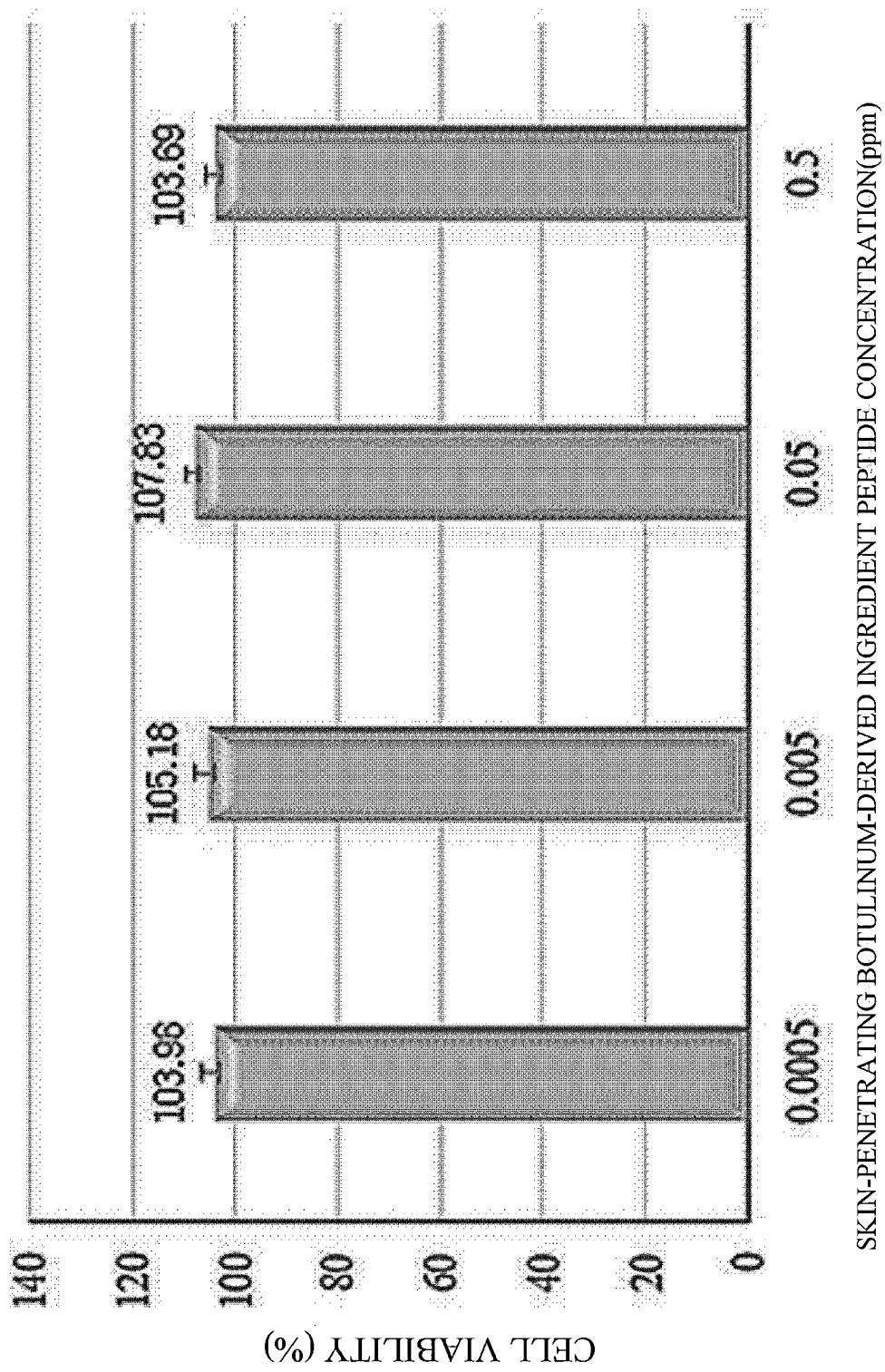


FIG. 4

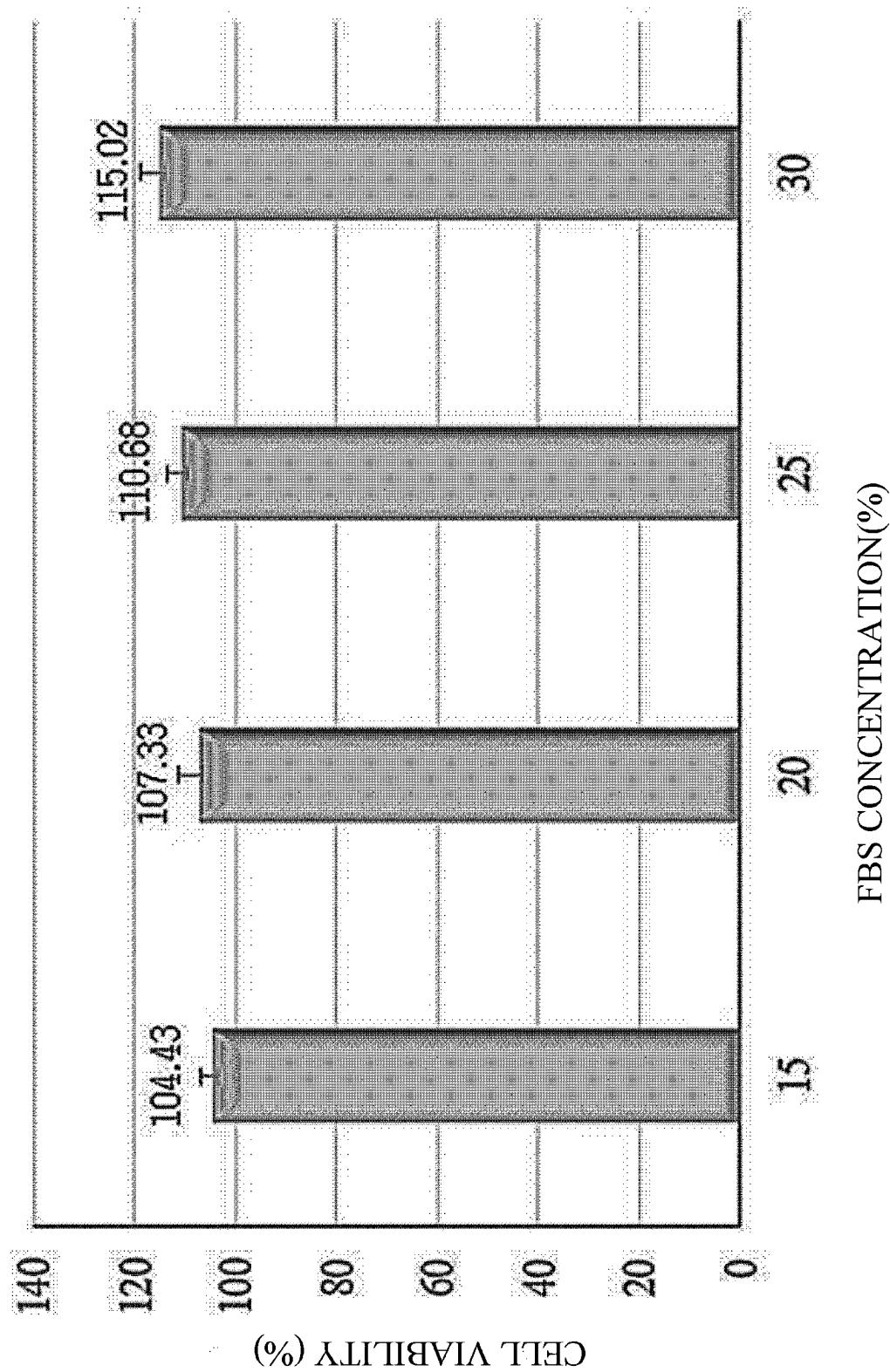


FIG. 5

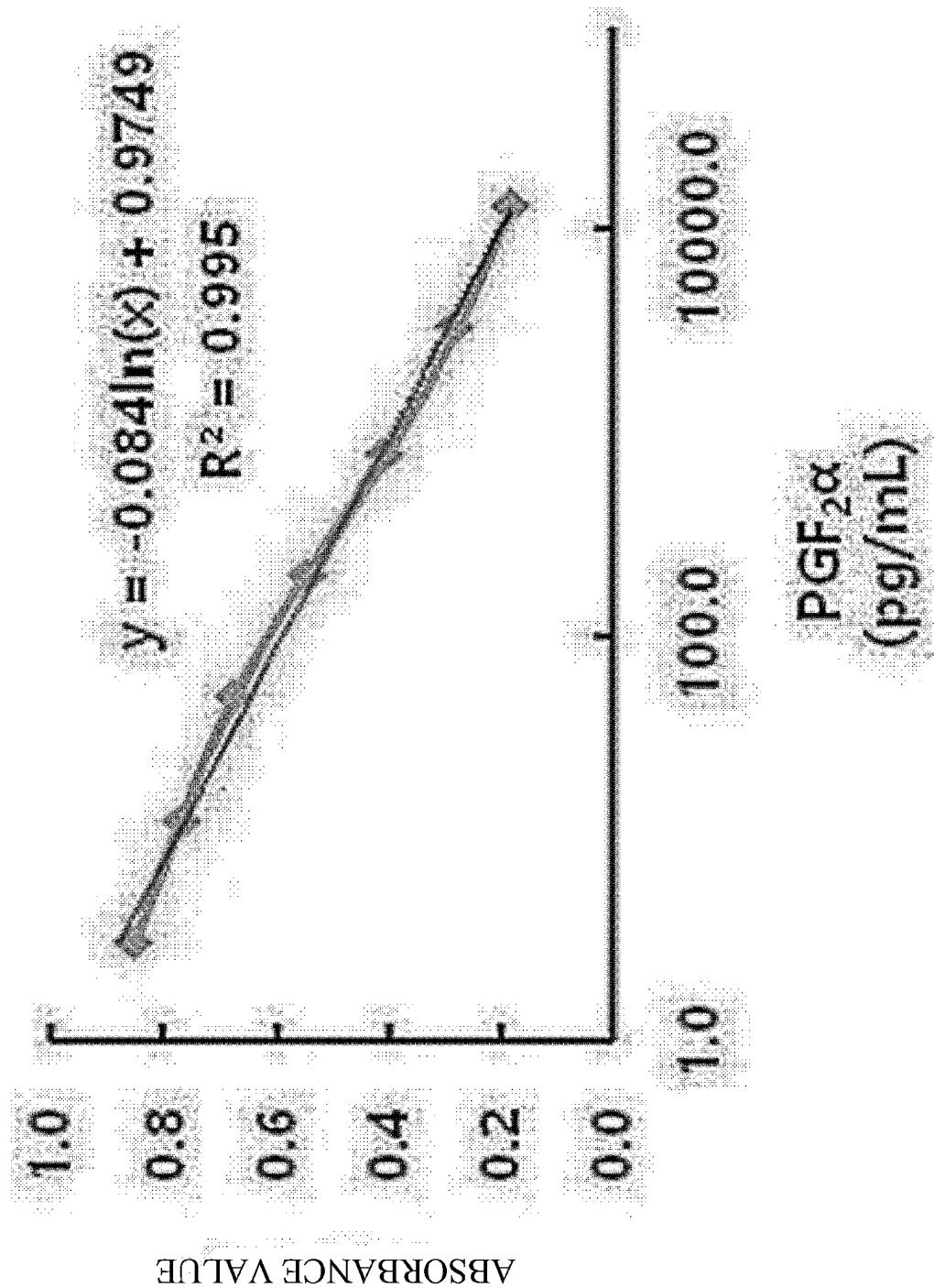


FIG. 6

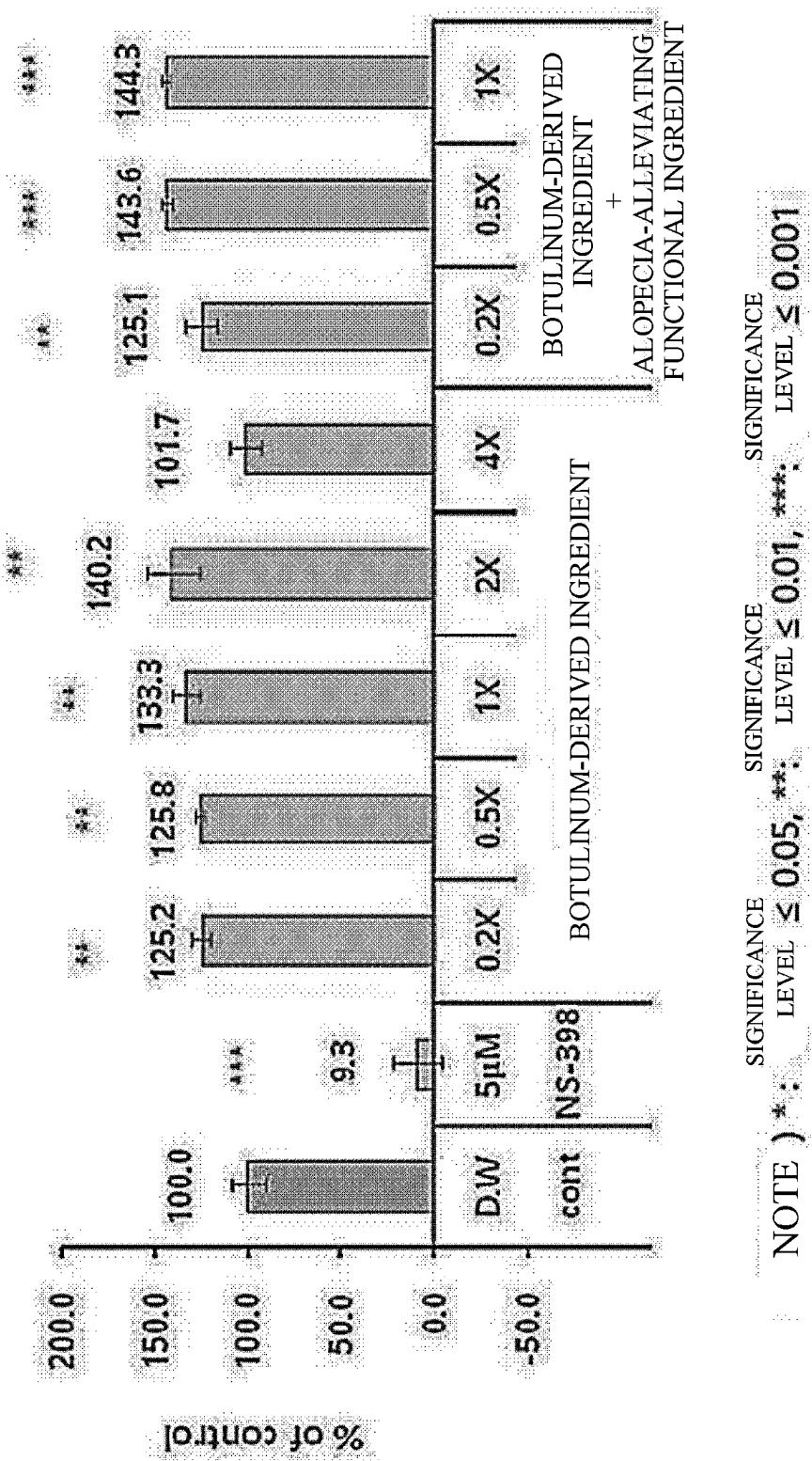


FIG. 7

SUBJECTS' SATISFACTION

PHOTO EVALUATION
BY EVALUATORS

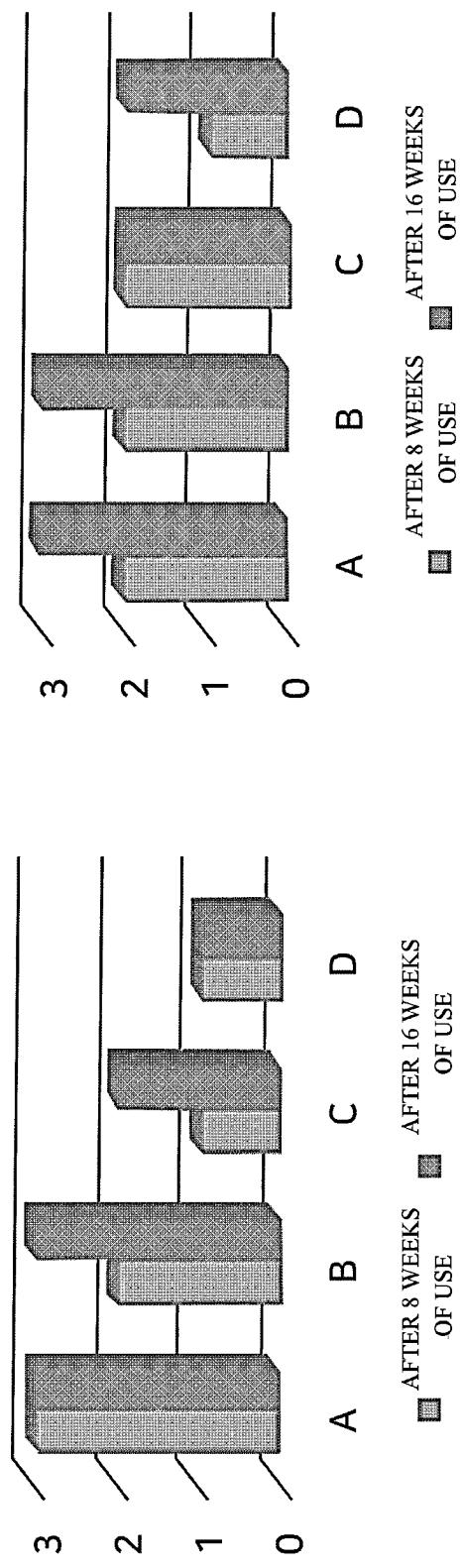
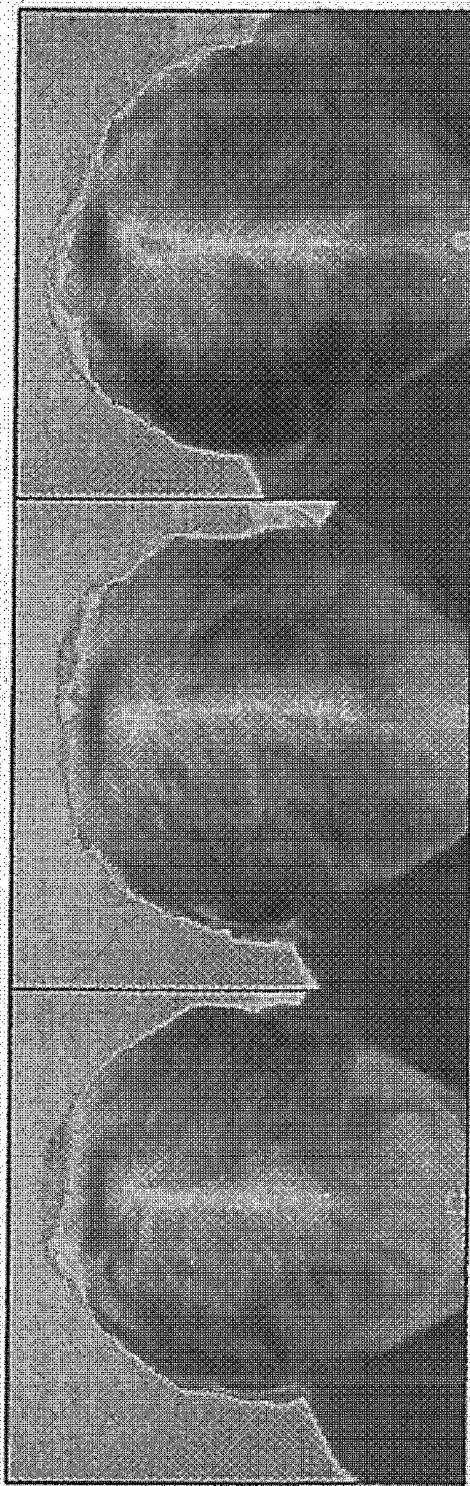


FIG. 8

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

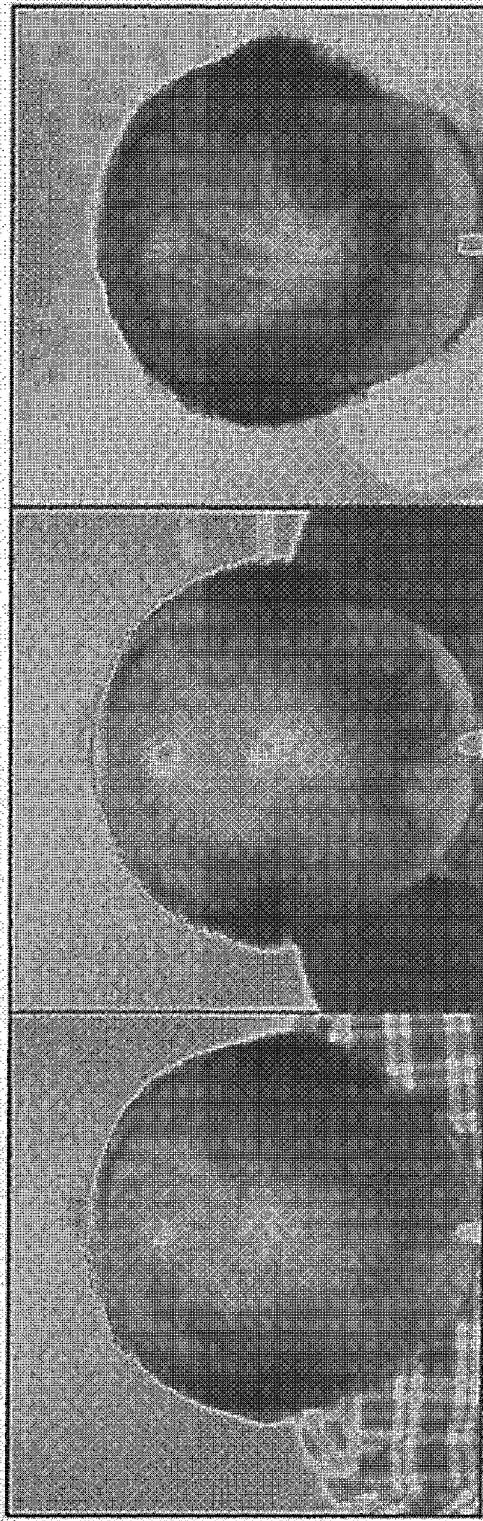


FIG. 10

SUBJECT C (50-YEAR OLD MAN)

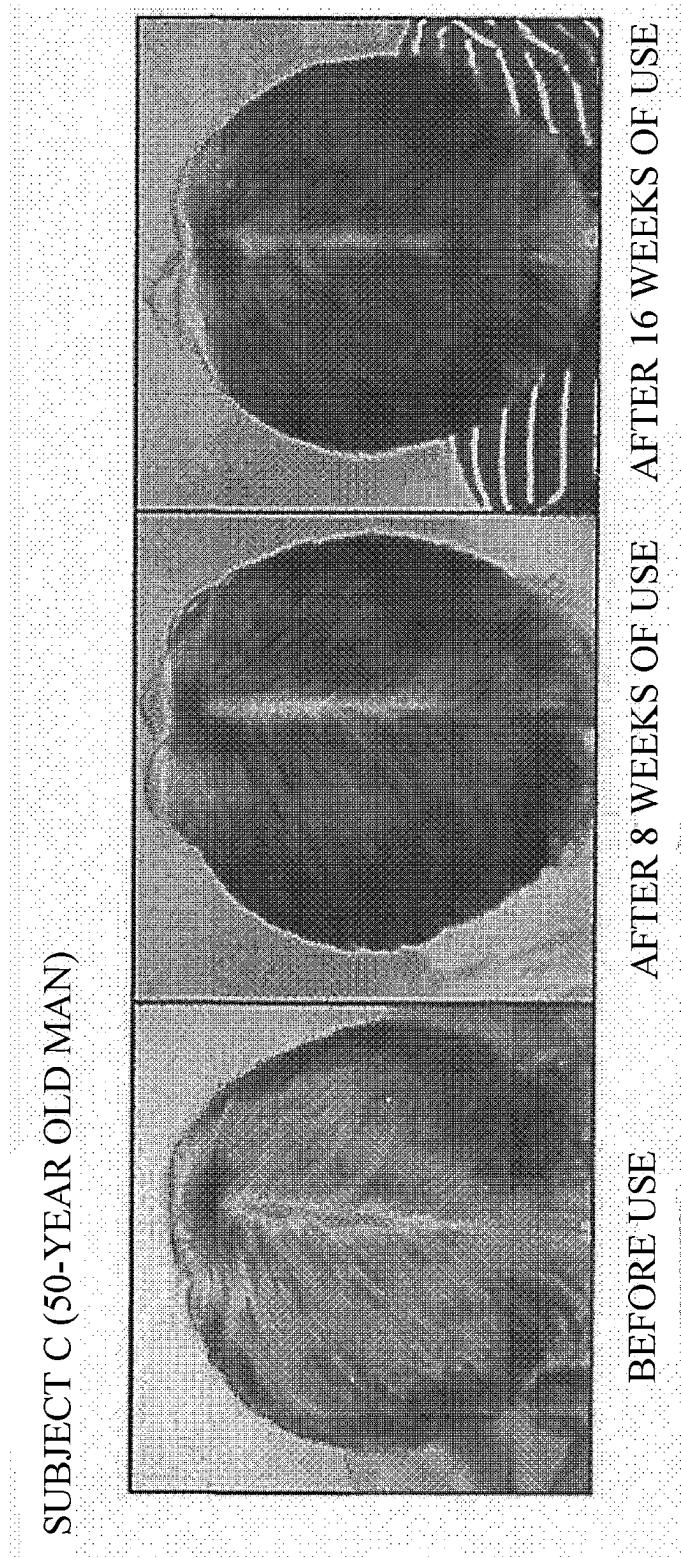
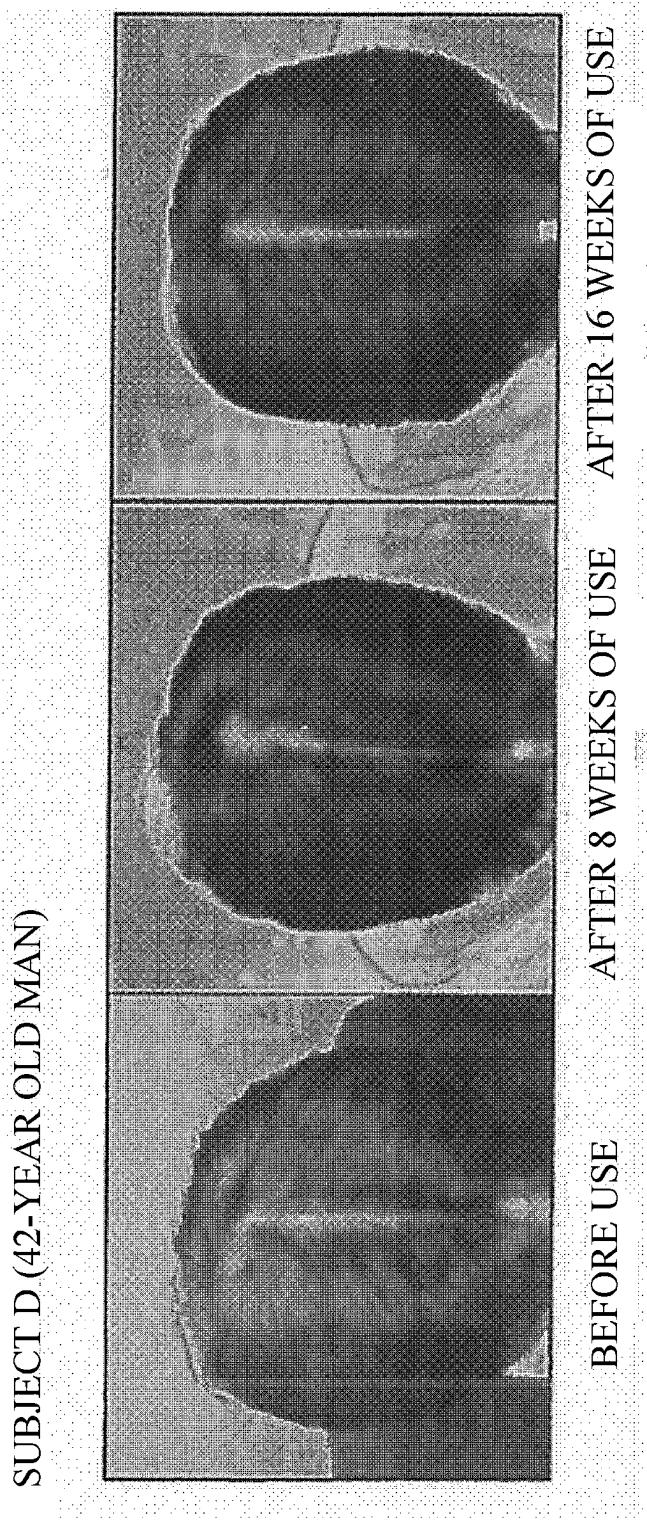


FIG. 11

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
KIHNIKIWWVPERDTFTNPEEGDLNPPPEAKQVPVSYYDSTYLSTDNEKD
NYLKGVTKLFERIYSTDLGRMLLTSIVRGIPFWGGSTIDTELKVIDTNC
INVIQPDGSYRSEELNLVIIGPSADIQFECKSFGHEVLNLTRNGYGST
QYIRFSPDFTFGFEESLEVDTNPLLGAGKFATDPAVTLAHELIHAGHRL
YGINAINPNRVFVKVNTNAYYEMSGLEVSFEELRTFGGGDAKFIDSLQENE
FRLYYYNKFKDIASTLNKAKSIVGTTASLQYMKNVPKEKYLLSEDTSKG
FSVDKLKFDFKLYKMLTEIYTEDNFVFKFFVKVLRKTYLNFDKAVFKINIV
PKVNYTIYDGFNLRNTNLAANFNGQNTIEINNMNFTKLKNFTGLFEEFYKL
LCVRGIITSKTKSLDKGYNKLEHHHHHH

-continued

```
ttcacgaagtgaagaactcaccggactttgagtttacaatttg
ctgtgtgtgcgcggatcatcaacttagaagaccaagagccttgcacaag
gctacaacaagtgactcgagcaccaccaccaccactga
```

[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 taaacataaa caagttctg 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.

SEQUENCE LISTING

```

Sequence total quantity: 86
SEQ ID NO: 1      moltype = AA  length = 13
FEATURE          Location/Qualifiers
source           1..13
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 1
KAMININKFL NQC

SEQ ID NO: 2      moltype = DNA  length = 39
FEATURE          Location/Qualifiers
source           1..39
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 2
aaggcgatga taaacataaa caagttcctg aaccagtgc

SEQ ID NO: 3      moltype = AA  length = 448

```

-continued

FEATURE	Location/Qualifiers
source	1..448
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 3	
MPFPVNQDFNY KDPVNGVDIA YIKIPNAGOM QPVKAFFIHN KIWVIPERDT FTMPEEGDLN 60	
PPPEAKQPVV SYYDSTYLST DNEKDNYLKG VTKLFERIYS TDLGRMLLTS IVRGIPFWGG 120	
STDIDTELKVI DTNCINVIQP DGSYRSEELN LVIIGPSADI IQFECKSFHG EVLNLTTRNGY 180	
GSTQYIRFSP DFTFGFEESL EVDTNPLLGA GKFKTDPAVT LAHELIHAGH RLYGIAINPN 240	
RVFVKVNTNAY YEMSGLEVS EELRTFGGGHD AKPIDSLQEN EFRRLYYYNKK KDIASTLNKA 300	
KSIVGTTASL QYMKNVFKEK YLLSEDTSGK FSVDKLKFDK LYKMLTEIYT EDNFVKFKV 360	
LNRKTYLNFD KAVFKINIVP KVNTIYDGF NLRNTNLAAAN FNGQNTSTEINN MNFTKLKNFT 420	
GLFEFYKLLC VRGIITSKTK SLDKGYNK 448	
SEQ ID NO: 4	moltype = AA length = 441
FEATURE	Location/Qualifiers
source	1..441
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 4	
MPVTINNFNY NDPIDNNNII MMEPPFARGT GRYYKAFKIT DRIWIIPERY TFGYKPEDFN 60	
KSSGIFNRDV CEYYDPPDYLN TNDKKNIFLQ TM1KLFNRNIK SKPLGEKLLE MIINGIPYLG 120	
DRRVPLEEFN CNIASVTVNK LISNPGEVER KKGIFANLII FGPGPVNLNE ETIDIGIQNH 180	
FASREGFGGI M0M0KFCPEYV SVFNNVQENK GASIFNRRGY FSDPA1LIMH ELIHVLHGLY 240	
GIKVDDLPV PNEKKFFMQS TDAIQAEELY TFGGQDPSII TPSTDKSIYD KVLQNFRGIV 300	
DRLNKVLVCI SDPNININIV KNKFKDKYKP VEDSEGKYSI DVESFDKLYK SLMFGPTETN 360	
IAENYKIKTR ASYFSDSLPP VKIRNLLDNE IYTIEEGFNI SDKDMEKEYR GQNKAINKQA 420	
YEEISKEHLA VYKIQMCKSV K 441	
SEQ ID NO: 5	moltype = AA length = 449
FEATURE	Location/Qualifiers
source	1..449
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 5	
MPITINNFNY SDPVDNKNIL YLDTHLNTLA NEPEKAFFR GNIWVIPDRF SRNSNPNLNK 60	
PPRVTPSKSG YYDPNLYLSTD SDKDPFLKEI IKLFRKRINR EIGEELIYRL STDIPFPGN 120	
NTPINTPDFD VDFNSDVKT RQGNNNVVKTG SINPSVIIITG PRENIIDPET STFKLTNTF 180	
AAQEFGFGALS IISISPRFEM TYSNATNDVG EGRFSKSEF MCPILILMHE LNHAMHNLYG 240	
IAIPNDQTIS TSVTSNIFYSQ YNVKLEYABII YAFCGGPTIDL IPKSARKYFE EKALDDYRSI 300	
AKRLLNSITTA NPSSFNKYIG EYKQKLIRKY RFVVEESSGEV TVNRNKFVEL YNELTQIFTE 360	
FNYAKIYNVQ NRKYLNSVY TPVTANILDD NVYDIQNGFN IPKSNLNVLF MGQNLRSRNP 420	
LRKVNPENML YLFTKFCHK A IDGRSLYNK 449	
SEQ ID NO: 6	moltype = AA length = 442
FEATURE	Location/Qualifiers
source	1..442
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 6	
MTWPVKDFNY SDPVNDNDIL YLRIPQNKLI TTPVKAFMIT QNIWVIPERF SSDTNPSLSK 60	
PPRPTSKYQS YYDPYSLSTD EQKDTFLKG I KLFKRINER DIGKKLINYL VVGSPFMGDS 120	
STPDETDFTF RHTTNIAVEK FENGSWKVTN IITPSVLIIFG PLPNILDYTA SLTLQGQQSN 180	
PSFEGFGTLS ILKVAPEFLL TFSVTSNQS SAVLGKSIFC MDVPIALMHE LTHSLHQLYG 240	
INIPPSDKRIR PQVSEGFFSQ DGPNVQFEEL YTFGGLDVEI IPQIERSQLR EKALGHYKDI 300	
AKRLLNNKNTK PSSWISNID KYKKIFSEKY NFDKDNTGNF VVNIDKFNSL YSDLTNVMSE 360	
VVYSSQYNVK NRTHYFSRH YLPVANILDD NIYTIRDGFN LTNKGFNIEN SGQNIERNPA 420	
LQKLSSESSEV DLFTRKCLL TK 442	
SEQ ID NO: 7	moltype = AA length = 422
FEATURE	Location/Qualifiers
source	1..422
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 7	
MPTINSFNYN DPVNNRTILY IKPGGCQQFY KSFNIMKNI IIPERNVIGT IPQDFLPPTS 60	
LKNGDSSYYD PNYLQSDQEK DKFLKIVTKI FNRINDNLNG RILLEELSKA NPYLGNDNTP 120	
DGDFIINDAS AVPIQFSNGS QSILLPNVII MGAEPEPDLFET NSSNISLRNN YMPSNHGFGS 180	
IAIVTFSPHEY SFRFKDNSMN EFIQDPALTL MHELIHSLHG LYGAKGITTK YTITQKQNPL 240	
ITNIRGTNIE EFLTFGGTDL NIITSAQNSD IYTINLLADYK KIASKLKVQ VSNPLLNPyK 300	
DVPEAKYGLD KDASIGIYSVN INKFNDIFKK LYSFTEFDLA TKFQVKCRQT YIGQYKVFKL 360	
SNLLNDSIYN ISEGYNINNL KVNFRGQNNAN LNPRIITPIT GRGLVKKIIR FCKNIVSVKG 420	
IR 422	
SEQ ID NO: 8	moltype = AA length = 436
FEATURE	Location/Qualifiers

-continued

-continued

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

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

SEQUENCE: 13

	organism = Synechococcus elongatus	
atgcacatggc	cagtaaaaaga ttttaatttat agtgatccgt ttaatgacaa tgatatatta	60
tatthaagaa	taccacaaaa taagttaatt actacacctg taaaagctt tatgattact	120
caaaatattt	gggttaatcc agaaaaggat tcatcgata ctaatccaag tttaaagttaaa	180
ccccccacac	ctacttc当地 gatcaaaatg tattatgatc ctgttattt atctatgtat	240
gaacaaaaaaag	atacattttt aaaagggatt ataaaattat tttaaaagaat taatgaaaga	300
gatataggaa	aaaatttaat aaattttta gtatgttgtt cacctttat gggagattca	360
agtacgcctt	aagatatact tgatgttaca cgtcatacta ctaatattgc agtgtaaaag	420
tttggaaaatg	gtatgttggaa agtaacaataatttataaacac caagtgttattt gatatttggaa	480
ccacttc当地	atataatttta ctatacagca tcccttacat tgcaaggaca acaatcaaataat	540
ccatcathtt	aagggtttgg aacattatct atactaaaag tagcacctga atttttgtta	600
acatttatgt	atgttaacatc taatcataatg tcagctgtat tagggcaatc tatattttgt	660
atggatccag	taatagttt aatgcatacg ttaacacatt ctttgcatac attatattggaa	720
ataaatatac	catctgatcaa aaggatgttcc ccacaatgtt gcggaggatt tttttctcaa	780
gatggaccca	acgttacaatt tgaggatatacatattt gaggatttaga tgggttggaaaata	840
atacctcaa	ttgaaagatc acaattaaaga gaaaaagcat taggttcaataaagatata	900
gcggaaaaagac	ttaataatataatataaaactt atcccttca ttgttggatttag taatataat	960
aaatataataa	aaatatttttc tgaaaatgtt aatttttgata aagataataac aggaaatttt	1020
gttgttataa	ttgataaaaat caatagcttatttgcatact tgactaatgt tttatgttggaaa	1080
gttgttattt	tttcgc当地ata taatgttaaa aacaggactc attatttttc aaggcattat	1140
ctacctgtat	ttgcaaatat attagatgtt aatattttata ctataagaga tgggtttaat	1200
tttacaaaataa	aagggttttaa tatagaaaat tcgggtcaga atatagaaaag gaatccctgc当地	1260
ctacaaaaggc	tttagttcaga aagtgttagta gattttatca caaaagtatg ttttaagat	1320
acaaaaaa		1326

SEQ ID NO: 14 moltype = DNA length = 1266
FEATURE Location/Qualifiers
source 1..1266
mol_type = other DNA

-continued

-continued

caaataatata	aaaataaaata	tgattttgtt	gaagatccta	atggaaaata	tagtgttagat	1020
aaggataagt	ttgataaatt	atacaggcc	ttaatgtttg	gctttactga	aactaatcta	1080
gctggtaat	atggaaaaa	aactaggat	tcttattttt	gtgaatattt	gccaccgata	1140
aaaactgaaa	aattgttaga	caatacaatt	tataactcaa	atgaaggcct	taacatacg	1200
agtaaaaatc	tcaaaaacgga	atthaatggt	cagaataagg	cggtaaataa	agaggcttat	1260
gaagaaaatca	gcctagaaca	tctcgttata	tatagaatag	caatgtgcaa	gcctgtatg	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 Y KDPVNQFDIA YIKIPNAGQM QPVKAFKIHN	60	
KIWIWPERDT FTNPPEEGDLN PPPEAKQPV SYYDSTYLST DNEKDNYLKG VTKLFERIYS	120	
TDLGRMLLTS IVRGIPFWGG STIDTELKVI DTNCINVQD GSYSRSEELN LVIIGPSADI	180	
IQFECKSFGH EVLNLTTRNGY GSTQYIRFSP DFTFGFEESL EVDTNPLLGA GKFAATDPAVT	240	
LAHELIHAGH RLYGIAINPN RVFKVNTNAY YEMSGLEVFSS EELRTFGGH AKFIDSLQEN	300	
EFLYLYYYNKF KDIASLNLKA KSIVGTTASL QYMKNVFKEK YLLSEDTSGK FSVDKLKFDK	360	
LYKMLTEIYT EDNFVKFFKV LNRKTYLNF D KAVFKINIVP KVNYTIYDGF NLRNTNLAA	420	
FNGQNTEINN MNFTKLKNFT GLFEPYKLLC VRGIITSKTK SLKDGYNK	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	
DRIWIIPERDFTFGYKPEDFN KSSGIFNRDV CEYYPDYLN TNDKKNIFLQ TMKLFNRIK	120	
SKPLGEKLLM MIINGIPYLG DRRVPLLEFN TNIASVTVNK LISNPGEVER KKGIFPANLII	180	
FGPGPVLNEN ETIDIGIQNH FASREGFGGI MQMKFCPEVY SVFNNVQENK GASIFNRRGY	240	
FSDPALILMH ELIHVLHGLY GIKVDDLPV PNEKKFFMQS TDAIQAEELY TFGGQDPSII	300	
TPSTDKSIYD KVLQNFRGIV DRLNQVLVCI SDPNININII KNKFKDKYKF VEDSEGKYSI	360	
DVESFDFKLYK SLMFGPTETN IAENYKIKTR ASYFSDSLPP VKIKNLLDNE IYTIEEGFNI	420	
SDKDMEKEYR GQNKAINKQA YEEISKEHLA VYKIQMCKSV K	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 PPRVTSPKSG YYDPNLYSTD SDKDPFLKEI IKLFRINSR	120	
EIGEELIYRL STDIPPPGNN NTPINTFDFD VDPNSVDVKT RQGNWWVKTG SINPSVIITG	180	
PRENIIDPET STFKLTNTNTF AAQEGFGALS IIISPRPML TYSNATNDVG EGRPSKSEFC	240	
MDPILILMHE LNHAMHNLGY IAIPINDQTIS SVTSNIFYQS YNVKLEYAEI YAFGGPTIDL	300	
IPKSARKYFE EKALDYRSI AKRRLNSITTA NPSSFNKYIG EYKQKLLRKY RFVVESSGEV	360	
TVNRRNKFVEL YNELTOIFTE FNYAKIYNQ NRKIYLSNVY TPVTANILDD NVYDIQNGFN	420	
IPKSNLNVL MGQNLRSNPA LRKVNPENML 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 SDPVDNDIL YLRIPQNKLI TPPVKAFMIT	60	
QNIWVIPERF SSDTNPLSLK PPRPTSKYQS YYDPSYSTD EQKDTFLKGK I KLFKRINER	120	
DIGKKLINAL VVGSPFMGDS STPEDTFDFT RHTTNIAVEK FENGSWKVTN IITPSVLIFG	180	
PLPNILDYTA SLTLOGQQSN PSFEGFGTLS ILKVAPEPLL TFSDVTSNQS SAVLGKSIFC	240	
MDPVIALMHE LTHSLHQLYG INIPSDKIR PQVSEGFPSQ DGPNVQFEEL YTFFGLDVEI	300	
IPQIERSK EKALGHYKDI IPSSWNINKT IPSSWISNID KYKKIFSEKY NFDKDNTGNF	360	
VVNIDKFNLSL YSDLTNVMSE VVYSSQYNVK NRTHYFSRHY LPVFANILDD NIYTIRDGFN	420	
LTNKGFIEN SGQNIERNPA LQKLSSESVV DLFTKVCLR 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 MPTINSFNY DPVNNRTILY IKPGGCQOFY KSFNIMKNIW	60	
IIIPERNVIGT IPQDFLPPTS LKNGDSSYYD PNYLQSDQEK DKFLKIVTKI FNRINDNLG	120	

-continued

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	VTRRTTSVNIK	LSTNVES SML	LNLLVLGAGP	180
DIFESCCYPV	RKLIDPDVVY	DPSNYGFGSI	NIIVTFSPEYE	YTFNDISGH	NSSTESFIAD	240
PAISLAHELI	HALHGLYGYAR	GVTYEETIEV	KQAPLMTAEK	PIRLEELTF	GGQDLNIITS	300
AMKEKIYNNL	LANYEKIATR	LSEVNSAPPE	YDINEYKDYF	QWKYGLDKNA	DGSYTVNENK	360
FNBIYKKLYS	FTESDLANKF	KVKCRNTYFI	KYEFLKVPNL	LDDDIYTVSE	GFNIGNLAVN	420
NRGQSIKLN P	KIIDSI PDKG	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 VANSINKK	IIQPGAEDQI	KGLMTNLII IF	180	
GPGPVLSDLNF	TDSMIMNGHS	PISEGFGARM	MIRFCPSCLN	VFPNVQENKD	TSIFSRRAYF	240
ADPALTLHM E	LIHV LHLGYG	IKISNLPITP	NTKEFFMQHS	DPVQAELYT	FGGHDPVIS	300
PSTDMDIYNNK	ALQNFQDIAN	R LNIVSSA QG	SGIDISLYKQ	IYKNKYD FVE	DPNGKYSVDK	360
DKFDKLYKAL	MFGFTETNLA	GEYGIKTRY S	YFSEYLPPKI	TEKLLDNTI Y	TQNEGFIAS	420
KNLKTEFNGQ	NKAVNKEAYE	EISLEHLVIY	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	cgtgtccag	atgcaacccg	ttaaggcatt	taaaatccat	180
aacaaaatct	gggttatccc	agagccggat	accttaccca	accccgagg	gggcgatctg	240
aaccccccgc	cggaggcga	gcagggtccca	gtgagactact	acatagacac	ctacctcagc	300
accgacaa	agaaggacaa	ctacctcaa	ggagtcaacg	agttgttca	gagaatctac	360
tccacagacc	tccggccat	gettctaacc	agcattgtgc	gtggcattcc	cttttggg	420
ggtctacca	tccgacacaga	gctyaagggt	atagacacca	actgcatcaa	cgtaatccag	480
cctgacggca	gctaccgaag	cgaggagct	aacctgggt	tcatcggccc	ttccggccat	540
atcatccat	tccgatgtca	gagtcggc	cacgggttc	tgaacctcac	ccggaaacggc	600
tatggaa	cccagtacat	aagattcago	cctgactca	ccttcgggtt	tgaggagagc	660
ttggaggctc	acacaaaccc	cctgtggaa	gcccggaa	gtcgcaactg	cccaagccgt	720
actctggcac	acgagctgt	ccacccgggt	caccgcctgt	acggcatacg	tataaacc	780
aacagggtgt	tcaaaatgtaa	caacaaacgt	tactatgaa	ttagccgcct	ggagggtgagc	840
ttcgaggagc	tgagaacgtt	cgggggacat	gatgcttaat	ttatcgacag	cctgcaggag	900
aacaggatca	ggctgtacta	ctacaataaa	tcaaggata	tagcggacac	tctgaacaag	960
gccaaggatca	tcgttaggcac	tactgcatcc	ctccagttata	tgaagaatgt	gttcaaagag	1020
aaataacctgc	tgagccgagg	taccagggt	aagttcaggt	tggataa	taatgtcgac	1080
aagctgtata	agatgtcac	cggaaatctac	accgaggata	atttcgttaa	gttctcaag	1140
gtcttgcac	ggaagaccta	cctgaacttc	gacaaggccg	tgttcaagat	caacatcg	1200
cctaaatgt	actacccat	ctacgacggg	ttaacctga	ggaacaccaa	cctggccgct	1260
aacttcaacg	ggcagaacac	agagatcaac	aacatgaaat	tcacgaagg	gaagaacctc	1320
acccgactgt	ttgaggctca	caattgtctg	tgtgtgcgcg	ggatcatcac	tagcaagacc	1380
aagagccctg	acaaggccta	caacaagtga	ctcgagcacc	accaccacca	ccactgaa	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	ctattgataa	taataatatt	120

-continued

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	tcaagaaaac	aaaggcgc当地	gtatatttaa	tagacgtgg	720
tattttcag	atccagccctt	gatattatgt	catgaactta	tacatgtttt	acatggat	780
tatggcatta	aagttagatgt	tttccaattt	gtaccaatgt	aaaaaaaaat	ttttatgc	840
tctacatcgat	ctataccaggc	agaadacta	tataatgttgc	gaggacaaga	ttccacgc当地	900
ataactccctt	ctacggataa	aagtatctt	gataaagtgg	tgcaaaat	tttagggata	960
gtttagatagac	ttaacaatgg	ttttagtttgc	atatacgatc	ctaactatcaa	tattatataat	1020
tataaaaat	aattttaaaga	taatataaaa	ttcggttgaag	attctggggg	aaaataatgt	1080
atagatgtat	aaagttttga	taaattatata	aaaagcttta	ttgttgggtt	tcacaaaaact	1140
aatatagcag	aaaattataa	aataaaaaact	agagtttctt	attttagtga	ttcccttacca	1200
ccagaaaaaa	taaaaaaaat	attagatataat	gaaatcttata	ctatagagga	agggtttaat	1260
atatctgtata	aagatatgttga	aaaagaatgtt	agaggctcaga	ataaaagctat	aaataaaaaac	1320
gctttagaag	aaatgtacaa	ggggatttt	gctgtatata	agatacaat	gtgtaaaaat	1380
gtttaactcg	agcaccacca	ccaccaccc	tga			1413

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

SEQUENCE: 26

atgggcagca	gccatcatca	tcatcatcac	agcagccgccc	tggtgcgcg	cggcagccat	60
atgatgcca	taacaattaa	caacttaat	tattcagac	ctgttgataa	taaaaatatt	120
ttatatttg	atactattt	aaatactacta	gctaatacg	ctgaaaaagg	cttgcgcatt	180
acagaaaaata	tatgggtat	acctgtataga	ttttcaagaa	atcttatacc	aaataaaaat	240
aaaccttcctc	gagttacaag	ccctaaaagt	ggtttattatg	atccttatta	ttttagtact	300
gattctgaca	aagatacatt	tttaaaagaa	attataaagt	tattttaaaag	aattttatct	360
agagaaaaat	gagaagaatt	aatatataga	ctttcgacag	atataccctt	tcctgggaat	420
acaatacttc	caattaatac	ttttgttattt	gatgtatatt	ttaaacatgt	tgatgtttaa	480
actagacaag	gtaacaactg	ggttaaaact	ggtagcataa	atcctagtgt	tataataact	540
ggccatctag	aaaaccattat	agatccgaa	acttctacgt	tttaaaatcc	taacaatact	600
tttgcggcac	aagaaggatt	tttgtgtt	tcaataattt	caataatcc	taggtttatg	660
tcacatata	gtatgcAAC	taatgtatgt	ggagggggta	gattttctaa	gtctgatattt	720
tgcatggatc	caataactaa	tttaatgtat	gaacttaatc	atgcaatgc	taattttat	780
ggaatagtc	taccaaata	tcaaacaatt	tcatctgtaa	cttagataat	ttttttatct	840
caataataatg	tgaattatgg	gtatgcagaa	atataatgt	ttggagggtcc	aactatagac	900
ttttatctca	aaatgtcga	gaaatattt	gaggaaaagg	cattggatta	ttagatgtt	960
atagctaaa	gacttaatag	tataactact	gcaaaatcc	caagctttaa	taaatatata	1020
ggggaaatata	aacagaaaact	tatttagaaag	tatagatctg	tagtagaaat	ttcagggtgaa	1080
gttacagttt	atcgtaat	ttttgtttag	ttatataatg	aacttacaca	aatattttata	1140
gaattttact	acgtctaaaat	atataatgt	caaaatatgg	aaatataatct	ttcaatgtta	1200
tatactccgg	ttacggcgaa	tatatttagac	gataatgtt	atgatataca	aaatggattt	1260
aatatatcc	aaagttaattt	aaatgtacta	tttatgggtc	aaaattttat	tgcgaaatcc	1320
gcatttaagaa	aagtcaatcc	tgaatataatg	ctttatattt	ttacaaaatt	tttgctatcaa	1380
qcaataatgt	qtagatcatt	atataataaa	ctcgacgacc	accacccca	ccacttqa	1437

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

SEQUENCE: 27 Organism = synthetic construct

atgggcgcga	gccatcatca	tcatcatcac	agcagccggcc	ttgttgcgcg	cggcagccat	60
atgatgacat	ggccagtaaa	agattttaat	tatagtgtac	ctgttaatga	caatgtatata	120
tttattttaa	gaataccaca	aaataaagtt	attactacac	ctgtaaaagc	ttttatgtatt	180
actcaaata	tttgggtat	accagaaga	ttttcatcg	atactaattc	aagttaatgt	240
aaacccccc	gacccatctc	aaagatatacc	agtttattatg	atccatgtta	tttatctact	300
gatgaacaaa	aagatacatt	tttaaaaggg	attataaaat	tattnaaaag	aattaatgaa	360
agagatatag	aaaaaaaatt	aataaaattat	tttagttagtt	gttcacccctt	tatgggagat	420
tcaatgtacg	ctgaatgatc	atttgatttt	acacgtcata	ctactaatat	tgcagtgtaa	480
aagtttgaa	atggtagtgt	gaaagttaaca	aatattataa	caccaagtgt	attgatattt	540
gacccatctc	ctaataattat	agactataca	gcacccctta	cattgcagg	acacaatca	600
aatccatcat	ttgaagggtt	tggacacatta	tctatactaa	aagttagcacc	tgaatttttg	660
ttaacattta	gtgtatgtaac	atctaataccaa	agttcaagctg	tattaggcaat	atctatattt	720
tgtatgtatc	cagtaataatgc	tttaatgtcat	gagtttacac	attttgttgc	tcaatttatat	780
ggaataataa	taccatctga	taaaaaggatt	cgtccacaag	tttagcgaggg	attttctct	840
caagatggac	ccaaacgttaca	atttgaggaa	tttatacat	ttggaggatt	aagtatgttga	900
ataataccctc	aaattgtaaaag	atcacaattta	agagaaaaag	cattaggatca	ctataaaagat	960

-continued

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	gtatgttata	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	tataatcat	ttaattttat	gaaaaatattt	180
tggataattc	cagagagaaa	tgtatgttgg	acaattcccc	aagttttctt	tccgctact	240
tcatgtaaaa	atggagatag	tagttttat	gaccctaattt	atttacaag	tgatcaagaa	300
aaggataat	ttttaaaaat	agtccacaaa	atatttaata	gaataaaatga	taatcttca	360
ggaaggattt	tatttgaaga	actgtccaaa	gtaatccat	attttagaaa	tgataatact	420
ccagatggtt	atccattat	taatgtatgc	tcagcgttcc	caatttcaattt	ctcaaatgg	480
agccaaagca	tacttattc	taatgttatt	ataatgggg	cagagcttgc	tttatttgaa	540
actaacatgt	ccaatatttc	tctaaagaaat	aatttatatgc	caagcaatca	cggttttgg	600
taatactgtt	tagtaacatt	ctcacctgaa	tattctttt	gatttaaaaga	taatagtatg	660
aatgaattt	ttcaagatcc	tgcttttca	ttaatgcatt	atttttttttt	tttatttttt	720
ggactatatt	gggctaaagg	gattactaca	agttactata	taacacaaa	acaaaatccc	780
cttataacaa	atataaagg	tacaaatattt	gaagaattctt	taactttttt	aggtactgtat	840
ttaacacata	ttactatgtc	tcagtc当地	gatattcttata	ctaatcttctt	agctgttatt	900
aaaaaaatgt	cgcttact	tagccaaatgt	caagtttcat	atccactact	taatctttat	960
aaagatgttt	tttgc当地	gtatggata	gataaaatgt	ctagcggat	ttttcggtt	1020
aatataaaaca	aattttaatga	tattttttaa	aaatttataca	gttttacgg	atttgttattt	1080
gcaactaaat	ttcaagttt	atgttggcaa	actttatattt	gacagtataa	atacttcaaa	1140
cttcaacaa	ttttttat	ttcttattttt	aatatatatgc	aaggcttataa	tataataat	1200
ttaaaaggtaa	attttagagg	acagaatgc	atttttaatc	ctgaaattt	tacaccaattt	1260
acaggtagag	gacttagttaa	aaaaatcatt	agattttgtt	aaaatattttt	ttctgttaaaa	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	ctgttaatga	tgatataattt	120
ttatacatatgc	agatattttat	tgaagaaaaaa	agttttttat	atttttttttt	tttttttttt	180
atgcgttaatgt	tttggataat	tcctggagaga	aattttttttt	tttttttttt	tttttttttt	240
gatccacccg	tttcattttaa	gaacggaa	agtttttttt	tttttttttt	tttttttttt	300
actgtatgtt	aaaaatgttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	360
agtaatcttgc	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	420
aatgaccacca	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	480
aaatttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	540
cttggatataat	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	600
tatgtatca	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	660
gaatatactt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	720
gatccctgca	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	780
agggggatgtt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	840
aaacccatata	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	900
agtgcgtatgt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	960
agacttagtg	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1020
tttcaatgtt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1080
aaattttatgt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	1140
ttttaaaatgtt	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		

-continued

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	ctatatttag	tagacgcgcg	720
tattttcgag	atccagctct	aacgttaatg	catgaactta	tacatgtgtt	acatggatta	780
atatggatata	agataagtaat	tttaccaattt	actccaaat	caaagaattt	tttcatgcaaa	840
catagcgatc	ctgtacaaagc	agaagaacta	tatacattcg	gaggacatga	tcctagtgtt	900
ataaagtctt	ctacggatata	gaatattat	aataaagcgt	tacaaattt	tcaagatata	960
gctaataatggc	ttaatattgt	ttcaagtgc	caagggagt	gaattgtat	ttccttat	1020
aaacaaatata	ataaaaataa	atatgatattt	gttgaagatc	ctaatggaaa	atatagtgt	1080
gataaggatata	atgttgatata	attatataag	gccttaatgt	ttggctttac	tgaaactaat	1140
ctagctgtt	aatatggatata	aaaaactagg	tattttttat	tttagtataa	tttgcacccg	1200
ataaaaactg	aaaaattgtt	agacaatata	atttataact	aaaatgtt	tttgcacccat	1260
gtctgttttt	atctcaaaac	ggaatttat	ggtcagaata	aggcggtaaa	taaagaggct	1320
tatgtatata	ttagccatgt	acatctcgat	atataatgaa	tagcaatgt	caagctgtt	1380
atgtacaaac	tcgagccacca	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	GHDAKFDSL	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	LNQCPVTINN	FNYNDPIDNN	NIIMMEPPFA	RGTGRYYKAF	KITDRIWIIP	60
ERYTFGYKPF	DFNKSSGIFN	RDVCHEYD	YLNTNDKNNI	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	KTGSIINPSVI	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		

-continued

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	QEYDKFLKIV	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	GARGVTYEET	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	LKTDAAEKDFK	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	EVDTNPLLGA	GKFATDPAVT	LAHELIHAGH	RLYGIAINPN	240
RVFKVNTNAY	EMMSGLEVSF	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

-continued

KSSGIFNRDV	CEYYDPDYLN	TNDKKNIFLQ	TMKLFNRIK	SKPLGEKLLE	MIINGIPYLG	120
DRRVPLEEFN	TNIASVTVNK	LISNPGEVER	KKGIFANLII	FGPGPVLNEN	ETIDIGIQNH	180
FASREGFGGI	MQMFKCPEVY	SFNNVQENK	GASIFNRRGY	FSDPALILMH	ELIHVLHGLY	240
GIKVDDLPV	PNEKKFFMQS	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						
MPITINNFNY	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	TKFQVKCRQ	T 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
DPSNYGFSI	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	P KIIDSIPDK	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

-continued

ASTPPDKFAA	NVANVSINKK	IIQPGAEDQI	KGLMTNLIIIF	GPGPVLSDNF	TDSMIMNGHS	180
PISEGFGARM	MIRFCPSCLN	VFNNVQENKD	TSIFSRRAYF	ADPAITLMHE	LIHVLHGLYG	240
IKISNLPITP	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
IYTEDNPFVFKF	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

-continued

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
LQEISYAKPY	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	GHSPISEKPGK	ARMMIRTSRR	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	SDPNININIVY	KNKFKDKEYKF	VEDSEGFYSI	360
DVESEFDKLYK	SLMFGFTETN	IAENYKIKTR	ASYFSDLPLP	VKIKNLLDNE	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	SDKDPFLKEI	IKLFKRINSR	120
EIGEELIYRL	STDIPPPGNN	NTPINTFDPD	VDPNSVVDVKT	RQGNNWWVKTG	SINPSVIITG	180

-continued

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 NVYDIQNQGFN	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
NSSNISLRRN YMPSNHGFGS IAIVTFSPEY SFERPKDNSMN EFIGQDPAITL MHELIHSLG	240
LYGAKGITT K YTITQKQPL I TNIIRGTNIE EFLTFGGTDL NIITSAQSNID 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 NIVTFSPPEE YTFNDISGHH NSSTESFIAD	240
PAISLAHELI HALHGHLGYAR GVTYEETIEV KQAPLMAIEK PIRLEEFPLTF GGQDLDNITS	300
AMKEKIYNNL LANEKIAITR LSEVNSAPPE YDINEYKDYF QWKYGLDKNA DGSYTVNENK	360
FNEIYKKLYS FTESDLANKF KVVKCRNTYFI KYEFLKVPNL LDDDIYTVSE GFNIGNLAVN	420
NRQOSIKLNP KIIDSPDKG LVEKIVKFCK SVIPRKCQNL FKNNINIMAK	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 TYGQPDQFNA STGVFSKDVY EYYDPTYLKT DAEKDKFLKT MIKLFNRINS	120
KPSGQRLLDM IVDAIPYLGK ASTPDKFAA NVANVSINKK IIQPGAEDQI KGLMTNLIIIF	180
GPGPVLSDNF TDSMIMNGHS PISEGFGARM MIRFCPSCLN VFNNVQENKD TSIFSRAYF	240
ADPALTLMHE LIHVVLHGLYK IKISNLPIPT NTKEFFMHOHS DPVQAEELYT FGGHDPSVIS	300
PSTDMNIYNNK ALQNFQDIAN RLNVSSAOG 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	
atgaaggcca tcatcaatata taacaaggta ttatcaatgtt gtcctttgt caacaaacag	60
ttcaactaca aggaccgagt taatggat gacatcgcat atatcaagat tcccaacgct	120
ggccagatgc aaccgcgttaa ggcatataaa atccataaca aaatctgggt tatcccagag	180

-continued

cgggataacct	tcaccaaccc	cgaggagggc	gatctgaacc	ccccgcggga	ggcgaagcag	240
gtcccagtga	gotactacga	tagcacccat	ctcagcacccg	acaacgagaa	ggacaactac	300
ctcaaaggag	tcacgaagtt	gttcgagaga	atctactcca	cagacctcg	ccgcatgctt	360
ctaaccacga	tttgtcgtgg	cattccctt	tggggcggtc	ctaccatcga	cacagagctg	420
aagggtgatag	acaccaactg	catcaacgt	atccagcctg	acggcagct	ccgaagcag	480
gagcttaacc	ttgtgtatcat	cggeccctcc	gccgatatac	tccaaatcga	gtgcaagagc	540
ttcggccacg	agggtcctgaa	cetcaccccg	aacggctatg	gaagcacca	gtacataaga	600
tttagccctt	acttcacccctt	cgggtttag	gagagcttgg	aggtegacac	aaacccctg	660
ctggggagccg	ggaagtgcgc	cactgaccca	gccgtgact	tgccacacga	gctgatccac	720
gcccggtaccc	gctgtacgg	catacgatata	aacccaaacaa	gggtgttcaa	agtgaacacc	780
aacgcttact	atgaardtag	cggcctggag	gtgagcttcg	aggagctgag	aacggtcggg	840
ggacatgatg	ctaaatttat	cgacacccgt	caggagaacg	agttcaggct	gtactactac	900
aataagtta	aggatatacg	gagcactctg	aacaaggcga	agtcctatcg	aggcactact	960
gcatccctcc	atgatgtatgg	gaatgtgtt	aaagagaat	acctgtcgag	cgaggatacc	1020
ageggtaagt	tcagcgtgga	taatgtttag	ttcgacaagc	tgtataatag	gctcaccggaa	1080
atctacaccg	aggataattt	cgttaagtcc	tcaagggtcc	tgaacccggaa	gaccatctg	1140
aacttcgaca	aggccgtgtt	caagatcaac	atcgtgccta	aagtgaacta	caccatctac	1200
gacgggttta	acctgaggaa	caccaacccgt	gccgctaaat	tcaacgggca	gaacacagag	1260
atcaacaaca	tgaatttac	gaagttgaag	aacttcacccg	gactgttga	gttctacaaa	1320
ttgctgtgt	tgcgccggat	catactagc	aagaccaaga	gccttgacaa	aggctacaac	1380
agtga						1386

SEQ ID NO: 60	moltype = DNA	length = 1362				
FEATURE	Location/Qualifiers					
source	1..1362					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 60						
atgaaggcoca	tgtcaatata	taacaagttc	ttaaatcaat	gtccagttac	aataaataat	60
ttaattata	atgatctat	tgataataat	aatattatta	tgatggagcc	tccatttgcg	120
agagggtacgg	ggagatatta	taaagctttt	aaaatcacag	atcgatattt	gataataccg	180
gaaagatata	cttttgata	ttaaacatgg	gattttataa	aaagttccgg	tattttaat	240
agagatgttt	gtgaatattt	tgatccagat	tacttaataa	ctaatgataa	aaagaataata	300
tttttacaaa	caatgatcaa	gttattttat	agaatcaat	caaaaccatt	gggtgaaaag	360
tttattttaga	tgattttataa	ttgttatactt	tatcttggag	atagacgtgt	tccactcgaa	420
gagtttaaca	caaacatgtc	tagttaact	gttaataat	taatcgtttaa	tccaggagaa	480
gttgagcgaa	aaaaaggtat	tttcgcaat	ttaataatata	ttggacccgg	gccagttt	540
aatgaaaatg	agactataga	tataggtata	caaatttattt	ttgcatcaag	ggaaggctt	600
gggggtataa	tgcaatgtaa	gttttgccta	gaatatgtaa	gcgttattaa	taatgttcaa	660
gaaaacaaag	gycgaatgt	atthaataga	cgtggatatt	tccatgatcc	agccttgata	720
ttaatgcat	aacttataca	tgttttatac	ttttttatgt	gcattaaatgt	agatgatata	780
ccaaatgtac	caaatgaaaa	aaaatttttt	atgcaatcta	catatgttat	acaggcagaa	840
gaactatata	cattttgggg	acaatgtcc	agcatatataa	ctcccttctac	ggataaaatgt	900
atctatgtat	aaagtttgc	aaattttttta	ggggatagtgg	atagactttaa	taatgttttta	960
gtttgcata	cagatcttaa	cattaatata	aatatataata	aaaataaaat	taaagataaaa	1020
tataaattcg	ttgaagattc	tgagggaaaa	tatagttatag	atgttagaaag	ttttgatataa	1080
ttatataaaa	gottaatgtt	ttgtttttata	gaaactataat	tagcagaaaa	ttataaataa	1140
aaaacttagag	tttctttttt	tagtgttcc	tttaccacca	aaaaataataaa	aaattttata	1200
gataatgaaa	tctatatact	agaggaaagg	tttataatata	ctgatataaga	tatggaaaa	1260
gaatatagag	gtcagaataa	agctataat	aaacaagctt	atgaagaaat	tagcaaggag	1320
cattttggct	tatataatag	acaaaatgtt	aaaagtgtt	aa		1362

SEQ ID NO: 61	moltype = DNA	length = 1386				
FEATURE	Location/Qualifiers					
source	1..1386					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 61						
atgaaggcoca	tgtcaatata	taacaagttc	ttaaatcaat	gtccaaataac	aattaacaac	60
ttaattattt	cagatcttgt	tgataataaa	aatattttat	attagatatac	tcatatataat	120
acactagcta	atgagcttga	aaaaggcttt	cgcattacag	aaaatataat	ggtaataacct	180
gatagatttt	caagaaattc	taatccaaat	ttaaataaaac	ctccctcgagt	tacaaggcc	240
aaaagggtttt	attatgtatcc	taattttttt	agttactgtt	ctgacaaaga	tacattttta	300
aaagaaatata	taaagtattt	taaaagaat	aatttcaat	aaataggaga	agaattataa	360
tatagactat	cgacagatata	accccttctt	ggaaataaca	ataacttataat	taataactttt	420
gattttgcata	tagttttaa	cagtgttgc	gtttaaaacta	gacaaggtaa	caacttgggt	480
aaaactggta	gcataaatcc	tagtgcata	ataacttggac	ctagagaaaa	cattataat	540
ccagaaactt	ctacgtttaa	attaaactaac	aatacttttgc	cgccacaaaga	aggatttgg	600
gttttatcaa	taattttat	atcacccat	ttttgttata	catatgtttaa	tgcaactaat	660
gatgttaggg	agggttagatt	ttcttaatgtt	gaattttgca	tggatccat	actaatttttta	720
atgcataac	ttaatcatgc	aatgcataat	tttatatggaa	tagtataacc	aaatgtatca	780
acaatttcat	ctgttaactag	taatattttt	tattcttataat	ataatgttga	attagatgtt	840
gcagaaatat	atgcatttgg	agggttcaact	atagacccat	tccctaaaag	tgcaaggaaa	900
tattttgagg	aaaaggcatt	ggattttat	agatctataat	ctaaaagact	taatgttata	960
actactgca	atccctcaag	ctttaataaa	tatatagggg	aatataaaaca	gaaacttatt	1020
agaaagatata	gatctgtatg	agaatcttca	ggtgaagtt	ctgatataat	taataatgtt	1080

-continued

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

atgaaggcca	tgatcaatat	taacaagttc	ttaaatcaat	gtacatggcc	agtaaaaagat	60
ttaatttata	gtgtatctgt	taatgacaat	gatataattt	atthaagaat	accacaaaat	120
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	taacacatcc	tttgcataat	ttatatggaa	taatataacc	atctgataaa	780
aggatttgtc	cacaagttt	cgagggtttt	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	ttgtttatcc	ttcgcaat	1140
aatgtttaaa	acaggactca	tttattttca	aggcattttt	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	gtccaaacaaat	taatagttt	60
aattataatg	atccgtttaa	taatagaaca	attttatata	ttaaaccagg	cggttgcata	120
caattttata	aatcattttaa	tattatggaa	aatatttgg	taatttccaga	gagaaatgt	180
atttgtacaa	ttccccaaga	tttttttccg	cttacttcat	tggaaaaatgg	agatagtat	240
tattatgacc	ctaattttat	aaaatgtat	caagaaaaag	ataaattttt	aaaaatagt	300
acaaaaatata	taatagaat	aatgtataat	ctttcaggaa	ggatttttt	agaagaactg	360
tcaaaagcta	atccatattt	aggaaatgt	aataactccg	atggtgactt	cattattaat	420
gtatgcattc	cagtttcaat	tcaatttctca	aatggtagcc	aaagcatact	atttcttaat	480
gttattataa	ttggggcaga	gcctgatata	tttggaaacta	acagttccaa	tatttctcta	540
agaaataat	atatgcctaa	caatcacgg	ttttggatcaa	tagctatata	aacattctca	600
cctgaatatt	cttttagatt	taaagataat	agttgtat	tttttttgc	atgttgcgt	660
tttacattaa	ttgtatgtt	aataccatca	tttacatggac	tatatggggc	taaagggtt	720
actacaaatgt	atatacttac	acaaaaacaa	atcccttaaa	taacaaat	aagggttaca	780
aatatttgc	aatttgcata	ttttggatgt	actgttata	acattttac	tagtgcctag	840
tccaaatgata	tctatactaa	tcttctatgt	gattataaa	aaatagcg	ttaacttgc	900
aaagtacaaat	tatctatcc	actacttta	ctttttaaa	atgttttgc	agcggatgt	960
ggatttagata	aaatgtctgt	cggtttat	tcggtaataa	taaacaatt	taatgtat	1020
ttttaaaaaat	tatatactt	tacggatatt	gatttagca	ctaaatttca	agttttatgt	1080
aggccaaatct	atatttgcata	gttataat	ttcaaaactt	caaacttgc	aatgtatct	1140
atttataata	tatcagaagg	ctataatata	aataatttta	agttttat	tagggacag	1200
aatgcataat	taaattccat	aattttata	ccaaatttgc	gttagggact	agtttttttt	1260
atcatttagat	ttttgtttat	tattttttct	gttttttttt	gttttttttt	gttttttttt	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	gtatgttt	gataatttct	180
gagagaaaata	caatggaaac	gaatccatgt	gttttgatc	caccggcttc	attaaagaaac	240

-continued

ggaaggcagt	cttattatga	tcctaaattat	ttaaccactg	atgctgaaaa	agatagat	300
ttaaaaacaa	cgataaaaatt	attnaagaga	attaataga	atccctcgagg	gaaattttg	360
ttacaagaa	tatcatatgc	ttaaccattt	ttagaaatg	accacacgc	aattgtat	420
ttcttcgg	ttaactgaaatc	tacaagtgtt	aatataaaat	tatcaactaa	tgttggaaatg	480
tcaatgttat	tgaatcttct	tgttattggga	gcaggacctg	atataatttga	aagtgttgtt	540
taccggat	gaaaactaat	agatccagat	gtatgtttatg	atccaatgtt	ttatggttt	600
ggataat	atatcgtgac	attttcac	gagttatgt	atacttttaa	tgatattatg	660
ggaggggata	atagtagatc	agaatcattt	atgcagatc	ctgcaatttc	actagtcat	720
gaattgtatc	atgcactgca	tggatttatac	ggggctaggg	gagttactta	tgaagagact	780
ataagaatgt	agcaagcacc	tttatgtata	gccgaaaaac	ccataaggct	agaagaattt	840
tttaacccttgc	gagggtcaggaa	ttttaatattat	attactatgt	ctatgagggaa	aaaaatataat	900
aaaaatctt	tagctaacta	tggaaaaata	gctactagac	tttagtgaagt	taatagtgt	960
cctccctgaat	atgatattaa	tgaatataaa	gatttttc	aatggaaatgt	tgggtctat	1020
aaaaatgtcg	atggaaatgt	tactgttaat	gaaaatataat	ttaatgtaaat	ttataaaaaaa	1080
tatataatgtt	ttacagagag	tgacttagca	aataatattt	aatggaaatgt	tagaatataact	1140
tattttattat	aatatgtat	ttttaaaatgtt	ccaaatttgt	tagatgtat	tattttatact	1200
gtatcagatc	ggtttaatat	agggttaat	gcagtaaaca	atcgccgaca	aagtataaaag	1260
ttaaatatgtt	aaatttattgt	ttccatttcca	gataaaaggtc	tagtagaaaa	gatcgataaa	1320
tttttqaaga	cgcttatttcc	taqaaaa				1347

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

SEQUENCE: 65

atgaaggcca	tgtatcaatat	taacaaggtc	ttaaaatccaat	gtccaggtaat	tataaaaanc	60
ttaattattd	atgaccctat	taataatgtat	gacatttata	tgtatggtaac	atccaatgcac	120
ccaggcccgac	gaacatata	taaaagttt	aggattatag	atcgatatttg	gatagttacca	180
gaaagggttta	cttagtgatt	tcaacctgac	caatttaatg	ccagtagcagg	agtttttagt	240
aaagatgtct	acgaatatta	cgtatccaa	tatttaaaaa	ccgtatgtca	aaaagataaa	300
ttttttaaaaa	caatgattaa	attttaat	agaatttatt	caaaaccatc	aggcacagaga	360
ttaactggata	tgtatgtaga	tgcataatct	tatcttggaa	atgcatactac	accggccgac	420
aaatttgcag	caaattgttgc	aaatgtatct	attaataaaa	aaattatcca	acctggagct	480
gaagatcaaa	taaaagggtt	aatgacaaat	ttaataatat	ttggaccagg	accaggctta	540
agtgtataat	ttactgtatag	tatgtattatg	aatggccatt	ccccatatac	agaggattt	600
ggtgcaagaa	tgtatgataag	attttgttct	agtgttttaa	atgtttaat	taatgttccag	660
gaaaataaaag	atacatctat	attttagtaga	cgcgcgtatt	ttgcagatcc	agctctaacg	720
ttaatgcatg	aacttatata	tgtgttacat	ggattatatg	gaattaaatg	aagtaatttta	780
ccaaattactc	caaataaaaa	aaattttctc	atgcacata	gcatctgt	acaaggcaga	840
qaactatata	catccggagg	acatgtatcc	agtgttataa	tcgttctac	ggatataatq	900
atttataata	aaggcttaca	aaattttca	gatatacgta	ataggcttaa	tatttttca	960
agtgcggcaag	ggagtggtat	tgtatattcc	ttatataaac	aaatataata	aaataatataat	1020
gattttgttg	aaatccat	ttggaaaattt	atgtgtat	aggataagtt	tgataaaat	1080
tataaggcc	taatgttttgc	ctttactgaa	actaaatctg	ctggtaata	tggaaaaata	1140
actaggatatt	tttatttttag	tgaatatttgc	ccacccgat	aaactgaaaa	attgttagac	1200
aataccat	atactccaaa	tgaagggttt	aaacatacta	gtttaaaatct	caaaacggaa	1260
ttaataatggtc	agaataaggc	ggtaaaaaaa	gagggtttag	aagaaatcag	ccttagaaat	1320
ctcggttat	atagaatagc	aatgtgcag	cctgtatgt	acaaa		1365

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

```

SEQUENCE: 66
atgccttttcaacaaca gttcaactac aaggcccgag ttaatggagt agacatcgca 60
tatatacaga ttccccacgc tgcccagatg caaccgtta aggcattaaa attcataac 120
aaaaatctggg ttatccccaga gccccggatacc ttccaccaacc ccgggggggg cgatctgaac 180
ccccccgggg aggccgaacga ggtcccccgtg agctactacg atagacaccta cttcagcacc 240
gacaacgaga aggacaacta cctcaaaagga gtcacaaagt tgttcgagag aatctactcc 300
acagacccctcg gccgcattgtc tctaaaccgc atttgccgtg gcattccctt ttggggccgc 360
tcttccatcc acacagacgt gaagggtgata gacaccaact gcataacacgt aatccagcet 420
gacggccggc accggaaaggc ggaggcttaaa ctgggtgtatca tggcccttc cgcgcgatatac 480
atccaatttcg agtgcacaaagg cttcgccac gagggtctga acctcacccg gaacggcttat 540
ggaaggcaccc agtacataag attcagccct gacttcaccc tgggtttgttggagagcttgc 600
gagggtcgaca caaaccccccgtggggagcc gggaaagtctcg ccactgaccc agccgtgact 660
ctggccacacgc agtctgtatcca cggccggccac ccgcctgtacg gcatacgat taaaacccaaac 720
agggttgttca aagtggaaacac caacgcgttac tatgaaatgatca gccggcttggaa ggttgcgttcc 780
gaggagctgta gaacgttccggggacatgtatca gttaaatttca tcgcacgcgttgcaggaaagaa 840
gagttcagggtgtactactca caataaggatcc aaggatatacgagactctga aacaaggcc 900
aagtccatcg taggcactac tgcattccctc cagttatgaa agaatgtgtt caaaagagaaa 960
tacctgtgttca gggaggatatac cagccggtaag ttcagctgtt aaatgcattaa gttcgacaaag 1020
ctgtatataaga tgctcacccaaatctacacc gaggataatt tgcgtttaaatttcttcaagggttcc 1080
ctgaaaccggaa agacctacttgc gaaatccggc aaggccgttgc tcaatgttcaa catcgctgtt 1140
aaaatgttcaacttgc acaccatctca cgacgggtttaaaccgttgc acaccaacccgttgc 1200

```

-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 ttttataataa 480
tttggacctg ggccaggat ttatggaaa gagaactatag atatggat acaaaatcat 540
tttgcataa gggaaaggctt cgggggtata atgcaatgt a gttttggcc agaatatgt 600
agcgttata ataatgttca agaaaaacaaa ggcgcaga tttttatag acgtggat 660
ttttcagatc cagccttgat attatcgtat gaaatatttac ttgttataa tggattat 720
ggcattaaatg tagatgtt accaatgtt ccaatgtaaa aaaaattttt tatgtcaatct 780
acagatgcta tacaggcaga agaactatata acatgttgg gacaagatcc cagcatcata 840
actcccttca cggataaaaag tatctatgt aaatgttgc aaaaattttt agggatagtt 900
gatagactta acaagggtttt agtttgcata tcagatcata acatataat taatataat 960
aaaatataat ttaaagataa atataatttcc gtttgcata ctgaggaaaa atataatgtata 1020
gatgtgaaa gttttgtata attatataaa agttaatgtt ttggtttac agaaaactat 1080
atagcagaaa attataaaat aaaaactaga gcttcttattt ttagtgcattt cttaccacca 1140
gtaaaaataa attatattttt agataatgtt atctataacta tagaggaa gtttataataa 1200
tctgtataaag atatggaaaa agaatatgtt ggtcagaata aagttataaa taaaacaaatgt 1260
tatgaagaaa ttagcaagga gcattttggcgtt gttatataa tacaatgtt taaaatgtt 1320
aatatgtcaaa atttatttcaaa gaacattaat atcatggccca 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 ttatgtat tcaagaaat ttaatccaa ttttataataa 180
cctccctcgat ttacaagccc taaaatgtt tttatgtat ctaattttt ggttactgtat 240
tctgacaaatg atacattttt aaaaatgtt ataaatgtt tttatgtat tttatgtat 300
gaataatgggg aagaatataat atatagactt tccgacagata taccctttcc ttggaaataac 360
aataactccaa ttaataactt ttatgttgc tttatgttgc acatgttgc ttgttataact 420
agacaaggta acaactgggt taaaactgtt agcataatc ttatgttgc aataactgtt 480
ccttagagaaa acattataga tccagaaact tctacgttta aattaactaa caaactttt 540
ggcgcacaaag aaggatgggg ttgtttatca ataaatccaa tttatgtat tttatgtat 600
acatataatgtt atgcaactaa ttatgttgc tttatgttgc tttatgttgc 660
atggatccaa tactatttt aatgtatca tttatgttgc tttatgttgc 720
atagctatac caaatgtatca aacaatttca ttgttacta gtaatatttt ttattctcaa 780
tataatgttca aattatgttca ttgttacta gtaatatttt ttattctcaa 840
attcccttcaaa gtcaggaa atatgttgc tttatgttgc tttatgttgc 900
gtctaaagac ttaatgttca aatctgttca gtttataataa atatgttgc 960
gaatataaaac agaaaactttagt agatgttgc tttatgttgc tttatgttgc 1020
acagtttttca gtaatattttt ttatgttgc tttatgttgc tttatgttgc 1080
ttaactatcg tttatgttca aatctgttca gtttataataa atatgttgc 1140
actcccttcaaa gtcaggaa atatgttgc tttatgttgc tttatgttgc 1200
atacctaaaa gtaatattttt ttatgttgc tttatgttgc tttatgttgc 1260
ttaagaaaatg tcaatcttcaaa atatgttca gtttataataa atatgttgc 1320
atagatgttca gtttataataa atatgttca gtttataataa atatgttgc 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 ttatgtacaa ttatgtat 60
tatatttataat tttatgttca tttatgttca tttatgttca tttatgttca tttatgttca 120
caaaatattttt ggttataacc agaaaatgtt tttatgttca tttatgttca tttatgttca 180
ccggcccgacat tttatgttca tttatgttca tttatgttca tttatgttca tttatgttca 240

-continued

gaacaaaag	atacatttt	aaaagggatt	ataaaattat	ttaaaaagaat	taatggaaaga	300
gatataggaa	aaaaattaat	aaatttatta	gtagtttgtt	caccttttat	ggggattca	360
agtacgcctg	aagatatact	tgattttaca	cgtcactata	ctaataattgc	agtgttggaa	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	aaaggattct	ccacaatgtt	gcggggatt	ttttctctaa	780
gtggggccca	acgtacaaat	tgaggatata	tatataattt	gaggattata	tgttggaaata	840
ataacctcaa	ttgaaagatc	acaattaaga	aaaaaaagcat	taggtcaacta	taaagatata	900
gcggaaaagac	ttaataatat	taataaaact	attcccttca	gttggatttag	taatataat	960
aaataataaa	aaatattttt	ttggaaaatgt	aattttgata	aagataataac	aggaaatttt	1020
gtttggaaaat	ttgataaaat	caataggtt	tattcagact	tgactaatgt	tatgttgcagaa	1080
gtttgtttat	cttcgcata	taatgttaaa	aacaggactc	attatttttc	aaggcattat	1140
ctacctgtat	ttgcaaaat	attagatgt	aatattttta	ctataagaga	tgggtttaat	1200
ttaacaaaata	aagggttttaa	tagataaaat	tcgggttcga	atataaaaag	gaatctctgca	1260
ctacaaaagc	ttagttcaga	aagtgtatgt	gattttat	caaaaatgt	ttaaagatgtt	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

```
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
ccccataaggc	tagaagaattt	tttacccctt	gggggttcagg	atttaataat	tattttatgt	840
gctatgaagg	aaaaaaatata	taacaatctt	tttagtcaact	atgaaaaaaat	agttacttaga	900
cttagtgaag	ttaatatgtc	tcctcctgtt	tatgatatttta	atgaatataaa	agattatTTT	960
caatggaaatg	atgggtctaga	taaaaaatgt	gatggaaatgt	atactgtaaa	tggaaaataaa	1020
tttaatgaaa	tttataaaaa	attatatagt	tttacagaga	gtgacttgc	aaataatTTT	1080
aaagtaaaaat	gtgaaatataat	tttattttttt	aaatataatgt	ttttttttttt	ttccaaattttt	1140
tttagatgtat	atattttatc	tgtatcagag	gggttttataa	taggttaattt	agcgttaaaac	1200
aatccgcggac	aaagtataaa	gtttaaatctt	aaaattttt	attccattcc	agataaaagg	1260

-continued

```
ctagtagaaa agatcgtaa attttgaag agcgttattc ctagaaatg tcaaaattha 1320
ttcaagaaca ttaatatcat ggcacag 1347
```

```
SEQ ID NO: 72 moltype = DNA length = 1365
FEATURE Location/Qualifiers
source 1..1365
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 72
atgccagttataataaaaan cttaattat aatgacccta ttaataatga tgacattatt 60
atgatggAAC cattcaatga cccaggGCa ggaacatatt ataaagctt taggattata 120
gatcgtaTTT ggatagtacc agaaaGGTT acttatggat ttcaacCTGA ccaatTTAAT 180
gccAGTAGC gagTTTTAG taaAGATGTC tacGAatATT acgatCCAC ttatTTAAA 240
accGATGCTG aaaaAGGAT ATTtTTAAAC acaatGTTA aattatTTAA tagaATTaaT 300
tcaAAACCAT caggACAGAG attactGGAT atgatAGTAt atGCTATAcc ttatCTTGGA 360
atGCACTTA caccGCCCGA caaATTGCA gcaatGTGG caaatGTtAc tattatTTAA 420
aaaATTATCC AACCTGGAGC tgaAGATCAA ataaaAGGTT taatGACAaA tttatATAA 480
tttggACCCG gaccAGTTCT aagtGATAAT tttaCTGATA gtatGTTA gaatGGCCT 540
tcccccaatAT cagaAGGATT tggTGAAGA atgatGATAA gatTTGTC tagTTGTTA 600
aatGTTATTA ataaGTTCA gggAAATAAA gatacATCTA tattttAGTAC acGCGCTG 660
tttgcAGATC cagCTCTAAC gttatGCA gaaCTTATAC atgtGTTACA tggattATAT 720
ggaATTAAAGA taAGTAAATTt accAACTTACT ccaaATAACAA aagaATTTT catGCAACAT 780
agcGATCCTG tacaAGCAGA agaACTATAT acatTCGGAG gacatGATCC tagTGTATA 840
agtCCCTCTA cggATGATTA TATTtTTATAA aAACGCTTAC aaaaTTTCA agatATAAGT 900
aaTAGGCTTA atATGTTTC aagtGCCCA gggAGTGGAA ttGATATTc cttatATAAA 960
caaATAATAA AAAATAATAA tgatTTGTT gaAGATCTA atGGAAATAA tagTGTAGAT 1020
aaAGGATAAGT ttGATAAATTt atataAGGcC ttaATGTTT gGTtACTGA aactAACTTA 1080
gctGGTGAAT atGGAATAAA aactAGGTt tCTTATTtTA gtGAATATTt gCCACCgATA 1140
aaaACTGAAA aattGTTAGA caataCAATT tataCTAA atGAAGGCTT taACATAGCT 1200
agtaAAAATC taaaaACGGA atTTAATGTT cagaATAAGG CGGTAAATAA agAGGCTTAT 1260
gaAGAAATCA gcoTGAACA tCTCGTTA tatAGATAAG caatGTGCAa gCCTGTAATG 1320
tacaATGTC AAAATTtTAA caagaACATT aataCTATG CCAAG 1365
```

```
SEQ ID NO: 73 moltype = DNA length = 1413
FEATURE Location/Qualifiers
source 1..1413
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 73
atgaaggCCA tGATCAATAT taacaAGTTc ttaaATCAAT gtCCCTTGT caacaACAG 60
ttcaactaca aggACCCAGT taatGGAGTA gacATCGCAT atATCAAGAT tCCCAACGCT 120
ggCCAGATGC AACCCGTTAA ggcATTAAATt accATAACAA aaATCTGGT tATCCAGAG 180
cgggatACCT tcAccAAACCC CGAGGAGGGC GATCTGAACC CCCGCCGGa ggcGAAGCAG 240
gtcccAGTGA tGACTACGA tagCACCCTA CTCAgCACCg acaACGAGAA ggacaACTAC 300
ctcaAAAGGAG TCACGAAGTT GTTCGAGAGA ATCTACTCCa CAGACCTGG CCgCATGTT 360
ctaAccAGCA TTGTCGTTG CATTCCCTT TGGGGCGGT CTACCATCGA CACAGAGCTG 420
aaAGTGTAGAT ACACCAACTG catCAACGCTA ATCCAGCTG ACGGCAGCTA CGGAAGCAG 480
gagCTTAACc TGGTGTACAT CGCCCTTC GCGGATATCA tccaATTGCA GTGCAAGAGC 540
ttcggCCACG AGGTCTGAA CCTCACCCGG AACGGCTATG GAAGCACCCA GTACATAAGA 600
ttcAGCCCTG ACTTCACCTT CGGGTTGAG GAGAGCTTGG AGGTGACAC AACCCCCCTG 660
ctgggAGGCG GGAAGTTGCG CACTGACCC GCGTGACTG TGGCACACGA GCTGATCCAC 720
gcccgtTCACC GCGTGTACGG CATAGCTATA AACCCAAACA AGGTGTTCAA AGTAAACACC 780
aacGCTTACT ATGAAATGAG CGGCTTGGAG GTGAGCTTC AGGAGCTGAG AACGTTCCGG 840
ggACATGATG CTTAAATTAT CGACAGCTG CAGGAGAACG AGTTCAAGGT GTACTACTAC 900
aaATAAGTCA AGGATATAGC GAGCACTG AACAAAGGCCA AGTCCATCTG AGGCACTACT 960
gcATCCCTC AGTATGTTAA GAATGTTG AGAGAGAAAT ACCTGTGTGAG CGAGGATACC 1020
agcGGTAAGT tcaGCTGTTA taGTTAAAG ttcGACAAGC TGTATAAGT GCTCACCGAA 1080
atCTACACCG AGGATAATTt CGTTAAGTTC tTCAGGTCC TGAACCGGA GACCTACCTG 1140
aactTCGACA AGGCGTGTt CAAGTCAAC ATCGTGCCTA AAGTGAACTA CACCATCTAC 1200
gacGGGTTA GACCGTGTGAA CACCAACCTG GCGCTAACT TCAACGGGA GAACACAGAG 1260
atcaACAAcA tGAATTTCAC GAAgTGAAG AACTTCACCG GACTGTTGA GTTCAACAA 1320
ttGCTGTGtG TGCGCGGGAT CATCACTGc AAGACCAAGA GCTTGACAA AGGCTACAC 1380
aagtGACTCG AGCACCACCA CCACCAACCAc TGA 1413
```

```
SEQ ID NO: 74 moltype = DNA length = 1389
FEATURE Location/Qualifiers
source 1..1389
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 74
atgaaggCCA tGATCAATAT taacaAGTTc ttaaATCAAT gtCCAGTTAC aataAAATA 60
tttaATTATA tGATCCTAT tgataATAAT aatATTATTA tGATGGAGCC tCCATTGCG 120
agAGGTACGG GGAGATTTA TAAAGCTTT AAAATCACAG ATCGTATTG GATAATACCG 180
gaaAGATATA CTTTGGATA TAAACCTGAG GATTTAAATA aAGTCCGG TATTTTAAT 240
agAGATGTT GTGAATTTA tGATCCAGAT TACTAAATA ctaATGATAA AAAGAATATA 300
tttttACAAaA CAATGATCAA GTTATTTAAT AGAATCAAAT CAAAACCAAT gggTgAAAAG 360
```

-continued

ttagatggata	tgattataaaa	tggtataccct	tatcttggag	atagacgtgt	tccactcgaa	420
gagggttaaca	caaacattgc	tagtgtaact	gttaataaaaat	taatcagtaa	tccaggagaa	480
gtggggccaa	aaaaagggtat	tttcgcacaaat	ttaataataat	ttggacgctgg	gccacgttta	540
aatggaaaatg	agactataga	tataggtaata	caaaatcatt	ttgcatacg	ggaaggcttc	600
gggggttataa	tgcaaatggaa	gttttgccca	gaatatgttaa	gcgttataa	taatgttcaa	660
gaaaacaaag	gcgcaagtat	attnaataga	cgtggatatt	ttttagatcc	agccttgata	720
ttaatgcatg	aacttataaca	tgttttacat	ggattatatg	gcattaaagt	agatgattta	780
ccaaatgttgc	caaatggaaaa	aaaattttttt	atgcatactca	cagatgtct	acagggagaa	840
gaactatata	catttggggg	acaagatccc	agcatcataa	cttccttctac	ggttataaagt	900
atctatgata	aagttttgc	aaattttaga	gggatagttt	atagacttaa	caaggtttta	960
gtttgcataat	cagatcctaa	cattaatatt	aatatataata	aaaataaatt	taaagataaaa	1020
tataaaattcg	ttgaagatc	tgaggggaaaa	tatagtatag	atgtagaaa	ttttgttataaa	1080
tatataaaa	gcttaatgtt	tgttttaca	gaaactataa	tagcagaaaa	ttataaaaata	1140
aaaacttagag	cttcttattt	tagtgatcc	ttaccacccag	ttaaaataaa	aaattttat	1200
gataatgaaa	tctatactat	agaggaaggg	ttaatataat	ctgataaaaga	tatggaaaaaa	1260
gaatataatag	gtcagaaataa	agctataataat	aaacaagctt	atgaaagaaa	taagcaaggag	1320
cattttggct	tatataagat	acaatgtgt	aaaagtgtaa	aactcgagca	ccaccacccac	1380
caccatgtca						1389

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

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

SEQUENCE:	76	atgaaggcca	tgtatcaatat	taacaaggtc	ttaaaatccaat	gtacatggcc	agtaaaaagat	60
ttaattattt	tgatcctgt	taatgacaat	gatataattat	atthaagaat	accacaaaat			120
aagttaatta	ctacacatgt	aaaagcttt	atgattactc	aaaaatatttgc	ggtaataccaa			180
gaaagagttt	catcagatac	taatccaagt	ttaagtaaac	cggccagacc	tacttcaaaag			240
tatcaaagt	attatgatcc	tagttattta	tctactgtat	aacaaaaaga	tacatttttt			300
aaagggat	taaaattattt	taaaaagatt	aatgaagag	atataggaaa	aaaattaat			360
aattatattt	tagttgttgtc	accttttatg	ggagatctaa	gtacgctgt	agatacattt			420
gat	ttttcacac	gtcataactac	taatatttgc	gttggaaaatgt	tttggaaatgg			480
gtaacaaata	ttataacacc	aagtgtat	atatttggac	cacttctaa	tatatttagac			540
tatacagcat	cccttacatt	gcaaggacaa	caatcaaatac	catcattgt	agggtttgg			600
acattatcc	tactaaaagt	agcacctgaa	ttttttgtt	cattttgt	tgttaacatct			660
aatcaaagt	cagctgtt	aggcaatact	atattttgt	tggatccat	aatagctt			720
atgcatgat	taacacatc	tttgcataccaa	ttttagtggaa	ttatataat	accatgtat			780
aggatcgctc	cacaagttag	cgaggatgtt	ttcttcttcaag	atggacccaa	cgtacaaattt			840
gaggaattat	atacattttg	aggattagat	gttggaaataa	tacctcaat	tgaaagatca			900
caattaagag	aaaaagcatt	aggtcactat	aaagatata	cgaaaagact	taataatatt			960
aataaaacta	ttcccttcttag	tttggatagt	aatatagata	aatataaaaa	aatatttttt			1020
gaaaagttt	attttgataa	agataataca	ggaaattttg	ttgttaataat	tgttaataat			1080
aatagctt	attcagactt	gactaatgtt	atgtcagaa	ttgttttattc	ttccgtcaat			1140
aatgtttaaaa	acaggactca	ttatTTTCA	aggcattatc	tacctgtatt	tgcataatata			1200

-continued

ttagatgata atatttatac tataagagat ggtttaatt taacaaataa aggtttaat
 atagaaaatt cgggtcagaa tatagaagg aatccgcac tacaaaagct tagttcagaa
 aagtgtatg atttatttac aaaagtatgt ttaagattaa caaaactcga gcaccaccac
 caccaccact ga 1260
 1320
 1380
 1392

SEQ ID NO: 77 moltype = DNA length = 1332
FEATURE Location/Qualifiers
source 1..1332
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 77
 atgaaggcca tgatcaatat taacaaggtc ttaaatcaat gtccaaataat taatagttt
 aatttataatc atccgtttaa taatagaaca attttatata ttaaaccagg cggttgc当地
 caattttata aatcatttaa tattatgaaa aatatttgc taatcccaga gagaatgt
 atggatcaa ttccccaga ttcttcccg cctacttcat tgaaaaatgg agatagtg
 tattatgacc ctaatttat acaaaggat caagaaagg ataattttt aaaaatgt
 aaaaaatattt ttaatagaat aatgataat ctccggaa ggattttt agaagaactg
 tcaaaagcta atccatattt agggaaatgt aatactcccg atgggactt cattattat
 gatgcatcg cagttcca tcaatttca aatggtagcc aaagcataact attaccta
 gtttattataa tggggcaga gcctgttca tttgaaacta acatgtccaa tatttctca
 agaaatattt atatgccaat caatcagggt ttggatcaat tagttatgt aacatttca
 ctggatattt ctggatattt taaagataat agtggatg aatttattca agatctgt
 cttagattt tgcatgattt aatacatca ttacatggac tataatgggc taaaggatt
 actacaaatg atactataac acaaaaacaa atcccttaa taacaaataat aagggat
 aatatttgc aatttcttaa ttttggatg actgttattt acattattac tagtgc当地
 tcaatgata tcttacttaa tcttcttgc gattttttt aatagctc taaaatgt
 aaagtacaag tatctatcc actacttaat ctttataaag atgttttga agcaagat
 ggatttagata aagatgtcg cggatattt tcggtaataa taaacaaatt taatgt
 ttttttttttatacagtt tacggattt gtttgc当地 ctaaaatccaa agtttattt
 aggcaaaactt atattggaca gtataatcc ttcaaaatcc ctaaaatgtt aatgtt
 atttataata tatacaggaa ctataatata aataatttaa aggttattt tagaggac
 aatgcaaaatt taaatccat aatttattaca ccaattacag gttagggact agttaaaaa
 atcatttagat ttgtttaaaa tttgttctt gtaaaaggca taaggctcga gcaccaccac
 caccaccact ga 60
 120
 180
 240
 300
 360
 420
 480
 540
 600
 660
 720
 780
 840
 900
 960
 1020
 1080
 1140
 1200
 1260
 1320
 1380
 1392

SEQ ID NO: 78 moltype = DNA length = 1374
FEATURE Location/Qualifiers
source 1..1374
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 78
 atgaaggcca tgatcaatat taacaaggtc ttaaatcaat gtccaggta aataatgt
 ttaatataatgaccctgt taatgtatg acaattttt acatgc当地 accatata
 gaaaaaaatg aaaaatattt taaagcttt gagattatgc gtaatgtt gataattc
 gagagaataa caataggaaac gaatccgt gatgttgc当地 caccggctt attaaggaa
 ggaaggcgtt ctttattatg tcccttaa ttaaccactg atgetggaaa agatagat
 ttttttttttatacagttt tacggattt gtttgc当地 ctaaaatccaa agtttattt
 aggcaaaactt atattggaca gtataatcc ttcaaaatcc ctaaaatgtt aatgtt
 atttataata tatacaggaa ctataatata aataatttaa aggttattt tagaggac
 aatgcaaaatt taaatccat aatttattaca ccaattacag gttagggact agttaaaaa
 atcatttagat ttgtttaaaa tttgttctt gtaaaaggca taaggctcga gcaccaccac
 caccaccact ga 60
 120
 180
 240
 300
 360
 420
 480
 540
 600
 660
 720
 780
 840
 900
 960
 1020
 1080
 1140
 1200
 1260
 1320
 1380
 1392

SEQ ID NO: 79 moltype = DNA length = 1392
FEATURE Location/Qualifiers
source 1..1392
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 79
 atgaaggcca tgatcaatat taacaaggtc ttaaatcaat gtccaggtaa tataaaaanc
 ttaatataatgaccctat taataatgt gacattttt tgatggaaacc attcaatgac
 ccaggcccgaaacatataa taaagctttt aggatttagt acgttattt gatgt
 gaaagggtttaa cttatggattt tcaaccctgc caatttatg ccagtacagg agt
 aaaaatgtctt acqatccact tattttttt ccqatqctq aaaaatgt
 60
 120
 180
 240
 300

-continued

tttttaaaaa	caatgattaa	attatTTTaa	agaattaatt	caaaaccatc	aggacagaga	360
ttactggata	tgatagtaga	tgctatcac	tatcttggaa	atgcatccac	accgccccac	420
aaatttgcag	caaATGTTGc	aatgtatct	attaataaaa	aaattatccca	acctggagct	480
gaagatcaa	taaaAGGTT	aatgacaaat	ttaataatat	ttggaccagg	accagtctta	540
agtgataatt	ttactgatag	tatgattatg	aatggccatt	ccccatatac	agaaggattt	600
ggTGcaagaa	tgatgataag	atTTTGTCT	agtTgtttaa	atgtatTTaa	taatgtttcg	660
gaaaataaaag	atACATCTAT	atTTGTTAGA	cgcgcgtt	ttgcagatcc	agctctaCG	720
ttaatgcatg	aacttataca	tgtgttat	ggattatATG	gaattaaGAT	aagtaatttA	780
ccaattactc	caaatacAAA	agaatTTTC	atgcaacata	gcgatCCTGT	acaAGCAGAA	840
gaactataat	cattcggagg	acatgatCT	agtGTTATAA	gtcCTTCAc	ggatATGAAT	900
atttataata	aaggcgttacA	aaatTTCAA	gatagatGTA	ataggCTTAA	tattgttca	960
agtGCCAAg	ggAGTGTGAAT	tgatATTCC	ttatataAC	aaatataAA	aaataAAAT	1020
gattttgttG	aaAGATCCTAA	tggAAAATAT	agtGTGATA	aggATAAGT	tgataAAATA	1080
tataaggcCT	taATGTTGG	cTTTACTGAA	actaatCTAG	ctggTGAATA	tggAAATAAA	1140
actaggTAT	cTTTATTTAG	tgtatTTG	ccaccGAA	aaACTGAA	attGTTAGAC	1200
aatacaATT	atACtAAAGA	tGAAGGCTT	aacatGCTA	gtaaaaATCT	caAAACGGA	1260
ttaatggcT	agaATAAGGC	ggtaATAAA	gaggCTATG	aagaAAATCAG	cCTAGAACAT	1320
ctcgTTATAT	atAGATAGC	aatgtGCAAG	cCTGTAATGT	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

atgggcagca	gocatcatca	tcatcatcac	agcagcggcc	ttgtgcggcg	cggcagccat	60
atGCCCTTG	tcaacAAACA	gttcaactac	aaggacCCAG	ttaatggagt	agacatcgca	120
tatatacaaga	tTCCCACGc	tggccagatG	caacCCGTTA	aggcatttaa	aatccataac	180
aaaatCTGGG	ttatcccAGA	gccccatacc	ttcaccaACC	ccgaggaggG	cgatCTGAAC	240
ccccCGCCG	aggcGAAGCA	ggTCCTGAGT	agetactacG	atagcaccta	cCTCAGCAC	300
gacaacGAGA	aggacAACTA	ccttAAAGGA	gtcAcGAAGT	tgttcgagAG	aatCTACTCC	360
acagacCTCG	gcccGATGCT	tcttaaccAGO	attgtgcgtG	gcattCCCTT	ttggggCGGC	420
tcttACCATCG	acACAGAGCT	gaaggTGTATA	gacaccaACT	gcatcaACGT	aatCCAGCCT	480
gacggcAGCT	acAGCAGCGA	ggagGTTAAC	ctggTGTATCA	tcggCCCTTC	cgCCGATATC	540
atccAACTCG	agtGCAAGAG	cttgcggcAC	gaggTCCGTA	accttACCCG	gaACGGCTA	600
ggaAGCACC	AGTACATAAG	attcAGCCCT	attcAcACTT	tcgggttGA	ggAGAGCTT	660
gaggTCGACA	caaACCCCT	gctgggAGGC	gggaAGTTCG	ccactgacCC	agCCGTGACT	720
ctggCACACG	ACGTGATCCA	cgcggcgtac	cgCCTGTACG	gcataGOTAT	aaACCCAAAC	780
aggGTGTTCA	AAGTGAACAC	caacGCTAC	tatGAAATGA	gccccTGTGA	ggTgAGCTT	840
gaggAGCTGA	GAACGTCG	gggACATGAT	gtcAAATTGA	tcgACAGCT	gcAGGAGAAC	900
gagttcAGGC	TGTACTACTA	caataAGTTC	aaggatATAg	cgAGCActCT	gaacaAGGCC	960
aaGTCCATCG	TAGGCACTAC	tgcAtCCCTC	cagtATATGA	agaATGTTGTT	caaAGAGAAA	1020
tacCTGTGTA	tgCAGGATAC	cAGCggTAAG	ttcAGCgtgg	ataAGCTTAA	gttgcACAAg	1080
ctgtATAAGA	TGCTCACCGA	aatCTACACO	gaggATAAT	tcgttAAAGTT	cttcAAAGGT	1140
ctgAACCGGA	AGACCTACCT	GAACtTCGAC	aaggCCGTG	tcaAGATCAA	CATCGTGCCT	1200
aaAGTGAACt	ACACCTACTA	cgcAGGTTAC	aacctGAGGA	acaccaACCT	ggCCGCTAAC	1260
ttaaACCGGG	AGAACACAGA	gatacAAACAD	atGAATTGTTA	cgaAGTTGAA	gaACTTCACC	1320
ggACTGTGTT	AGTTCTACAA	attGtGtGt	gtgcgcggGA	tcatcactAG	caAGACCAAG	1380
AGCCTTGAC	AGGCTACAA	caAGTGTATG	caaAATTAT	tcaAGAACAT	taataTCATG	1440
gccaAG						1446

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

SEQUENCE: 81

atgggcagca	gocatcatca	tcatcatcac	agcagcggcc	ttgtgcggcg	cggcagccat	60
atGCCAGTTA	caataATAAA	tttaattat	aatgtatCCTA	ttgataATAA	taatattATTA	120
atgtatGGAC	ctccATTGc	gagAGGTACG	ggggAGATAT	ataaaGCTT	taaaATCACA	180
gatcgtATT	ggataATAcc	ggAAAGATAT	actTTTGGAT	ataAAACCTGA	ggATTTAAT	240
aaaAGTTCCG	gtatTTTAA	tagAGATTT	tgtGAATATT	atGATCCAGA	ttacttAAAT	300
actaaTGTATA	aaAAGATAAT	atTTTACAA	acaATGATGA	AGTTTAACTTA	TAGAACTAAA	360
tcaAAACCTA	TGGGTGAAAA	gttattAGAG	atGTTATAcc	ttatCTTGG	420	
gatAGACGTG	ttccACTCGA	AGGTttaAC	acaAAACATTG	ctAGTGTAC	tgttAAATAA	480
ttaatcAGTA	ATCCAGGAGA	AGTGGAGCGA	aaaaAAAGGT	tttCgcoAAA	ttaataATAA	540
tttggacCTG	GGCCAGTTT	AAATGAAAT	gAGACTATAG	ATATAGGTAT	ACAAAATCAT	600
tttgcATCAA	GGGAAGGCTT	CGGGGTTA	ATGCAATGA	AGTTTGCCC	AGAATATGTA	660
AGCgttATTA	ATAATGTTCA	AGAAAACAAA	GGGCGAAGTA	TATTTATAG	ACGTGGATAT	720
ttttcAGATC	CAGCCTGAT	ATTAATGCA	GAACtTATAC	ATGTTTACA	TGGATTATAT	780
GGCATTAAAG	TAGATGATT	ACCAATGTA	CCAAATGAA	AAAATTTT	TATGCAATCT	840
ACAGATGCTA	TACAGGCGA	AGAACTATAT	ACATTGGAG	GACAAGATCC	CAGCATCATA	900
ACTCCTCTA	CGGATAAAAG	TATCTATGAT	AAAGTTTGC	AAAATTTAG	AGGGATAGTT	960
GATAGACTTA	ACAAGGTTT	AGTTGCTA	TCAgATCCTA	ACATTAATAT	TAATATATAT	1020
AAAATAAAAT	TAAAGATAA	ATATAAATT	GTGAGGAT	CTGGGGAAA	ATATAGTATA	1080

-continued

gtatggaaaa gttttgataa attatataaa agcttaatgt ttgggtttac agaaaactaat 1140
atagcggaaa attataaaaat aaaaactaga gcttcttatt tttagtgattt cttaccacca 1200
gtaaaaataa aaaattttt agataatgaa atctatacta tagaggaaagg gttaataata 1260
tctgtatataa atatggaaaa aaaaatataaa ggttcagaata aagctataaaa taaacaaggt 1320
tatgtggaaa tttagcaagga gcattttggt gtatataaga tacaataatgtg taaaagtgtt 1380
aaaatgtcaaa atttattccaa gaacattaaat atcatggcca ag 1422

SEQ ID NO: 82 moltype = DNA length = 1446
FEATURE Location/Qualifiers
source 1..1446
mol_type = other DNA
organism = synthetic constru

```

SEQUENCE: 82
atgggcgca gccatcatca tcatcatcac agcagggcg tggtgcgcg cggcagccat 60
atggccaata caattaacaa cttaattatc tcgatcctg ttgataataaa aaatatttt 120
tatttagata ctcattaaa tacatagtt aatgagctg aaaaaggctt tcgcattaca 180
ggaaatataat gggtaatacc tgatagattt tcaagaattt ctaatccaaa tttaaataaa 240
cctcctcgag ttacaagccc taaaagtgtt tattatgatc ctaattattt gagtactgtat 300
tcgtacaaag atacattttt aaaagaattt ataaaaggttt tttaaaagaat taattcttqa 360
gaaataggag aagaatttaat atatacgatc tcgacagata taccctttc tgggataaaq 420
aatactccaa ttaatacttt tgattttgat gtgatatttta acagtgttga tgttttaact 480
agacaaggta acaactgggt taaaactgtt agcataatac ctgtgttat aataactggta 540
ccttagagaaa acattataga tccagaaact tctcgttta attaactaa caatactttt 600
gcggccacaat aaggattttgg tgctttatca ataatttcaa tatccatctg attttatgtca 660
acatatgtt atgcacaaatc tgatgttggaa gagggtagat ttctcaatgc tgaattttcg 720
atggatccaa tactaattttt aatgcatgaa cttaatcatg caatgcataa ttatatatggta 780
atagctataac caaatgatca aacaatttca tctgtacta gtaatattttt ttatcttcaa 840
tataatgttga aatttagatgg tgcagaaata tatgcatttgg gagggttcaac tatagaccc 900
attccctaaaatgtcaggaa atattttggaa gaaaaggcat tggttattttat tagatctata 960
gctaaagac ttaatagat aactactgca aatccttcaat gctttataaa atataatagg 1020
gaatataaac agaaaactttat tagaaagtat agattcgttag tagaatcttc aggtgaagg 1080
acagatctttat gtaataatgg tttgttggaa tataatggactt ccacaaatatttacagaa 1140
ttttaactacg cttaaatataat taatgttacaa taatggaaaa tatatcttcaatgttat 1200
actcccggtta cggcgaatattt attagagcat aatgtttatg atataaaaa tggatattat 1260
atacctaaaa gtaattttaaatgttactattt atgggtcaaa atttatctcg aaatccagca 1320
ttaaaggaaatg tcaatcctgaaatatgttca tttttttttaaaaatttttgc tataaaagca 1380
atagatgttgc gatcattata taataatgtt caaaaattttatc tcaagaacat taatatcatg 1446
qccaaq

```

```
SEQ ID NO: 83          moltype = DNA    length = 1425
FEATURE              Location/Qualifiers
source                1..1425
                      mol_type = other DNA
                      organism = synthetic construct
```

SEQUENCE:	83	organism = Synechococcus elongatus				
atgggcagca	gccatcatca	tcatcatcac	agcgaggccc	tggtgcccg	cggcagccat	60
atgacatcg	cagtaaaaga	ttttaatatt	atgtgatctg	ttatgacaaa	tgatataat	120
tatthaaga	taccacaaaa	taatgttaatt	actacacccgt	taaaaagctt	ttatgttact	180
caaaatattt	gggtataacc	agaaaagattt	tcatcagata	ctaattccaag	tttaagtaaa	240
ccgcggcagac	ctacttcaaa	gtatcaagaat	tattatgtatc	ctagtattt	atctactgtat	300
gaacaaaaaa	aatcattttt	aaaagggatt	ataaaatattat	ttaaaagaat	taatgaaaaaa	360
gatataggaa	aaaatttaat	aaatattat	gtatgttgtt	cacctttat	gggagatttc	420
agtacgcctg	aagatacatt	tgatTTaca	cgtcatacta	ctaattattgc	agttgaaaag	480
tttggaaaatg	gtatgtggaa	agtaacaat	attataaac	caagtgtt	gatatttgg	540
ccacttcata	atataattaa	gtatcaga	tccttacat	tgcgaaggaca	acatcaaat	600
ccatcatgtt	aaagggtttgg	aacattat	atataaaag	tagcactgt	atttttgtta	660
acatTTtagt	atgttaacatc	taatcaa	tcagctgtat	taggcaaaatc	tatattttgt	720
atggatccag	taatagctt	aatgcatgg	ttaacacatt	cttgcatac	attatatgg	780
ataaataatac	catctgtat	aaaggatctgt	ccacaagttt	gcgagggatt	tttctctaa	840
gtatggccca	acgtcaattt	tgaggatata	tatataattt	gaggattata	tgttgttaaa	900
atacctcaaa	ttgaaagatc	acaattaaga	aaaaaaagcat	taggtcacta	taaagatata	960
gcgaaaaagac	ttaataat	taataaaact	attcccttca	gttggatttt	taatataat	1020
aaatataaaa	aaatattttt	ttgaaaatgt	aattttgata	aagataaatac	aggaaatttt	1080
gttgttataa	ttgtataaaat	caatagttt	tatttcagact	tgactaatgt	ttatgttcaaa	1140
gttgttattt	cttcgcata	taatgttaaa	aacaggactc	attatttttc	aaaggcattat	1200
ctacctgtat	ttgcaaatat	attagatgtat	aatattttata	ctataagaga	tggttttat	1260
tttacaaaata	aaaggttttaa	tatagaaaat	tcgggtccaga	atataaaaaag	gaatctctgca	1320
ctacaaaaggc	ttagttcaga	aaagtgtat	gattttat	caaaaatgtat	tttaagattt	1380
acaaaatgtc	aaaatttttatt	caaaacat	aatatcatq	ccaaad		1425

SEQ ID NO: 84 moltype = DNA length = 1365
FEATURE Location/Qualifiers
source 1..1365
mol_type = other DNA
organism = synthetic construct

SEQUENCE : 84

-continued

atgggcgcga	gccatcatca	tcatcatcac	agcaggccc	tggtgcgcgcg	cggcagccat	60
atgccaaca	taataatgtt	taattataat	gatccgttta	ataatagaac	aatttttat	120
attaaccac	gccccgttca	caaattttt	aaatccat	attatgtat	aaatatttgg	180
ataattccag	agagaaaatg	aatttgtaca	atttcccaag	attttcttc	gcctactca	240
ttgaaaaatg	gagatgttag	tttattatgc	cctaattatt	tacaaagtga	tcaagaaaag	300
gataaaat	taaaaatagt	cacaaaaata	ttaatagaa	taaatgataa	tcttcagga	360
aggattttat	tagaagaatg	gtccaaagct	aatccatatt	taggaatga	taatacttca	420
gatggtgact	tcattattaa	tgtatgcata	gcagtgttcaa	tcaattctc	aaatggtagc	480
caacgatcac	tattctttaa	tgttattata	atggggacag	agcttgttatt	atttggaaact	540
aacagttcca	atatttctc	aagaataat	tatatgcca	gcaatcacgg	ttttggatca	600
atagctatag	taacattctc	acctgtat	tcttttagat	ttaaagataa	tagtatgtat	660
gaatttttac	aagatccgtc	tttatcacat	atgcatgaat	taataccat	attacatcgat	720
ctatatgggg	ctaaagggtat	tactacaaag	tatactataa	cacaaaaaca	aaatcccccta	780
ataacaataa	taagggatc	aaatatttga	gaatttttaa	cttttggaggd	tactgtat	840
aacatttata	ctagtgtca	gtccaaatgt	atctatacta	atcttcttgc	tgattataaa	900
aaaatagcgt	cttaaacttag	caaagtacaa	gtatccatc	cactactta	tcccttataa	960
gatgtttttt	aagccaaatg	tggatgtat	aaagatgtca	gccccgttta	tccggttaat	1020
ataaaacaaat	ttatagatat	ttttaaaaaa	tttatacgat	ttacggaaat	tgatgtatgc	1080
actaaatttc	aagttaaatg	taggcaaaact	tatattggac	agtataaata	cttcaaaactt	1140
tccaaacttgt	taatgtatc	tattttataat	atatccaga	gtctataataa	aaatatttta	1200
aaaggtaat	ttagaggaca	gaatgtcaaa	ttaaattctt	gaattttac	accatttaca	1260
ggtagaggac	tagtaaaaaa	aatcatttga	ttttgtaaaa	atatttttc	tgtaaaaaggc	1320
ataaggtgtc	aaaatttatt	caagaacatt	aatatcatgg	ccaaag		1365

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

```

SEQUENCE: 86
atgggcgca gcccatac tcatcatac agcagcgcc ttgtgcgcg cggcagccat 60
atgcaggta atataaaa cttaattat aatgcaccta ttaataatga tgacattatt 120
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
tcccccaatattt cagaaggattt tggtgcagaagaa atgatgtataa gattttgcc tagttgttta 660
aatgtatattt atatagttttgc gggaaaataaa gatacatctt tatttttgttgc acggcgcgtat 720
tttgcagatc cagctcttaatc gttatgtatc gaatcttatac atgtgttaca tggattat 780
ggaaatgttgc taatgtatattt accaaatattt cccaaatataa aagaatgttgc catgttgcacat 840
agcgtatctgttacaaggcaga agaacttatat acatcggttgc gacatgtatcc tagttgttta 900

```

-continued

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	aactaggat	tcttatttta	gtgaatattt	gccaccgata	1200
aaaactgaaa	aattgttga	caatacaatt	tatactcaa	atgaaggctt	taacatagct	1260
agtaaaaatc	tcaaaacgga	atthaatggt	cagaataagg	cggtaaataa	agaggcttat	1320
gaagaaatca	gcttagaaca	tctcggtata	tatagaatag	caatgtcga	gcctgtatg	1380
tacaatgtc	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.

* * * * *