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(54) Title: NON-PHYSIOLOGIC DNA FRAGMENTS FOR TANNING SKIN

(57) Abstract: Compositions and method for protecting the skin from UV-damage and for sunless tanning, which contain as an active agent a non-physiologic DNA fragment analog, which is substantially stable against degradation by skin enzymes, yet still increases melanin production by melanocytes.

NON-PHYSIOLOGIC DNA FRAGMENTS FOR TANNING SKIN

The present invention relates to compositions and methods for sunless tanning and for protecting the skin from photodamage by applying to the skin a modified DNA fragment analog which is resistant to hydrolysis by skin enzymes, yet stimulates melanin production.

To many Caucasians a tan provides a pleasing and desirable appearance to skin. However, the long-term risks associated with excessive sunlight exposure, such as skin cancer, and photoaging make sun-tanning unappealing. Therefore, methods to increase skin pigmentation without exposure to damaging UV rays are highly desirable.

Skin color in humans is due largely to the abundance of a brown/black pigment, melanin, that is produced in the basal epidermis by specialized cells called melanocytes. Melanocytes transfer melanin to adjacent keratinocytes where it serves to protect cellular DNA from UV-induced damage by virtue of its ability to absorb UV-radiation. When skin is exposed to UV light as found in sunlight, melanin synthesis increases, as does the transfer of melanin to the keratinocytes, resulting in a visual darkening of skin color, known as a tan.

Double-stranded DNA fragments, deoxynucleotides and single stranded DNA such as thymidine dinucleotide (pTpT) have previously been disclosed to increase pigmentation in mammalian cells and induce tanning - a photoprotective

response - in skin (US 5,470,577; US 5,532,001; US 5,580,547; US 5,643,556). Unfortunately, topical application of DNA is problematic, since skin contains enzymes which hydrolyze DNA, before it can reach melanocytes.

Modifications which render DNA resistant to enzymatic attack are known in the art. WO99/60167 describes pharmaceutical or cosmetic compositions containing at least some of such modified DNA molecules. The present invention is based at least in part on the surprising discovery that at least some of such modified enzyme-resistant DNA fragment analogs retain their ability to stimulate melanin production by melanocytes. Previous DNA-based sunless tanning methods were based on simulating the physiological process, and thus employed physiological DNA fragments. It is surprising that even when modified to deviate from their physiological structure, DNA fragments still evoke the same physiological response from melanocytes.

The present invention includes a skin care composition comprising, in a cosmetically acceptable vehicle, a non-physiologic DNA fragment which

- remains at least 80% intact after 1 hour at 37°C in a skin homogenate assay; and
- increases melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay.

The invention also includes methods for sunless tanning and for protecting skin from the damaging effects of UV radiation, e.g., dry, wrinkled, and sagging skin.

The following non-limiting detailed description and the examples illustrate some of the effects of the inventive compositions.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material or conditions of reaction, physical properties of materials and/or use are to be understood as modified by the word "about." All amounts are by weight of the composition, unless otherwise specified.

The term "skin" as used herein includes the skin on the face, neck, chest, back, arms, hands, legs, feet and scalp.

For the avoidance of doubt the word "comprising" is intended to mean including but not necessarily consisting of or composed of. In other words the listed steps or options need not be exhaustive.

The term "non-physiologic DNA fragment analog" as used herein means a DNA analog molecule which is not naturally occurring within the human body.

Non-physiologic DNA fragment analog

Non-physiologic DNA fragment analogs suitable for use in the present invention must satisfy two criteria: they must remain at least 80% intact after 1 hour at 37°C in a skin homogenate assay, yet they must also increase melanin production by melanocytes (in vitro melanogenesis test).

Skin Homogenate Assay:

Non-physiologic DNA fragment analogs suitable for use in the present invention must remain at least 80%, preferably at least 85%, and most preferably at least 90%, intact after 1 hour at 37°C in a skin homogenate assay. The assay is described in detail in Example 3 below.

Melanogenesis test

The DNA fragment analog must increase melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay. The assay may be as described in Example 4 below. The preferred DNA fragment analogs increase the in-vitro melanin production by melanocytes by at least 20%.

Many types of non-physiologic DNA fragment analogs may be included in the present invention, as long as they satisfy the two tests described above and may be selected from the following DNA fragment analogs: phosphathioates phosphorodithioate, phosphorothiolates, phosphoramidate, alkyl or aryl phosphonates (e.g.methylphosphonate) boranophosphates, boranophosphorothioates and combinations of such linkages. These modifications may be internal (some or all of the linkages modified) and/or at the 5′ end of the fragment. In each case, oligonuclotides should possess a terminal 5′ charged functionality, preferably phosphate or modified phosphate (as above). This 5′ terminal group may optionally be covalently linked to cholesterol or fatty

groups (chain lengths 2-24 carbon atoms, either saturated (e.g. palmitic) or with varying degrees of unsaturation (e.g. oleic, linoleic) to promote cellular uptake and/or enhance stability.

In addition to modification of the internucleotide linkage, the nucleic acid bases and sugar moieties may also be modified. For example, 2'-O-methylnucleoside, 2'-O-thionucleoside and 2'-O-allylnucleoside may all be incorporated into the modified fragments, either partially or completely replacing the deoxyribose sugars.

Any of the above non-physiologic DNA fragment analogs may be used in the present invention, as long the analog passes the skin homogenate assay and also satisfies the melanogenesis test described above. Combinations of DNA fragments, which may also optionally be UV-irradiated, can also be used.

Generally, DNA fragment analogs included in the present invention contain from 2 to 100 nucleotides (or modified nucleotides). Preferably, however, in order to improve the penetration of stratum corneum, so that the DNA fragment analog can act on melanocytes, the DNA fragment analogs included in the present invention contain less than 10, or even more preferably less than 8 nucleotides, optimally from 2 to 8 nucleotides (or modified nucleotides).

The non-physiologic DNA fragment analog is employed in the present composition in an amount of from 0.001 to 20 wt.%, preferably from 0.01 to 10%, most preferably from 0.1 to 5wt.%.

The inventive compositions preferably include a sunscreen and/or chelating agent, or nuclease/phosphatase inhibitors in order to further improve the performance of the composition. Sunscreens provide additional protection against photodamage, while chelating agents and the inhibitors further improve the stability of the non-physiologic DNA fragment analogs.

Sunscreens

Sunscreens include those materials commonly employed to block ultraviolet light. Illustrative compounds are the derivatives of PABA, cinnamate and salicylate, titanium dioxide and zinc oxide. For example, avobenzophenone (Parsol 1789®) octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone (also known as oxybenzone) can be used. Octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone are commercially available under the trademarks, Parsol MCX and Benzophenone-3, respectively. The exact amount of sunscreen employed in the compositions can vary depending upon the degree of protection desired from the sun's UV radiation; generally the amount is from 0.1 to 10 wt.%, preferably from 1 to 5 wt.% .

Chelating Agent

Metal chelators increase the stability of the non-physiologic DNA fragments by inhibiting nuclease activity, especially cosmetically acceptable amount of metal chelators with strong affinity for magnesium and zinc. A group of

these chelators includes, but is not limited to, citrate, o-phenanthroline, ethylenediaminotetraacetic acid (EDTA), DTPA, ethylenedioxy-diethylene-dinitrilo-tetraacetic acid (EGTA), 8-hydroxyquinoline, nitrilotriacetic acid, tartaric acid.

The formulation may also include phosphatase and/or nuclease inhibitors including but not limited to levanisole tartrate, fluoride, methyl xanthines.

Chelating agent and or nuclease/phosphatate inhibitors may suitably be present in an amount of from 0.1 to 20%, preferably from 1 to 5%.

Cosmetically acceptable vehicle

The vehicle may be aqueous, anhydrous or an emulsion. Preferably, the compositions are aqueous or an emulsion, especially water-in-oil or oil-in-water emulsion. Water when present will be in amounts which may range from 5 to 99%, preferably from 20 to 70%, optimally between 35 and 60% by weight.

Besides water, relatively volatile solvents may also serve as carriers within compositions of the present invention. Most preferred are monohydric C1-C3 alkanols. These include ethyl alcohol, methyl alcohol and isopropyl alcohol. The amount of monohydric alkanol may range from 1 to 70%, preferably from 10 to 50%, optimally between 15 to 40% by weight.

Emollient materials may also serve as cosmetically acceptable carriers. These may be in the form of silicone oils and synthetic esters. Amounts of the emollients may range anywhere from 0.1 to 50%, preferably between 1 and 20% by weight.

Silicone oils may be divided into the volatile and non-volatile variety. The term "volatile" as used herein refers to those materials which have a measurable vapor pressure at ambient temperature. Volatile silicone oils are preferably chosen from cyclic or linear polydimethylsiloxanes containing from 3 to 9, preferably from 4 to 5, silicone atoms. Linear volatile silicone materials generally have viscosities less than about 5 centistokes at 25°C while cyclic materials typically have viscosities of less than about 10 centistokes. Nonvolatile silicone oils useful as an emollient material include polyalkyl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers. The essentially non-volatile polyalkyl siloxanes useful herein include, for example, polydimethyl siloxanes with viscosities of from about 5 to about 25 million centi-stokes at 25°C. Among the preferred non-volatile emollients useful in the present compositions are the polydimethyl siloxanes having viscosities from about 10 to about 400 centistokes at 25°C.

Among the ester emollients are:

(1) Alkenyl or alkyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include isoarachidyl

neopentanoate, isononyl isonanonoate, oleyl myristate, oleyl stearate, and oleyl oleate.

(2) Ether-esters such as fatty acid esters of ethoxylated fatty alcohols.

(3) Polyhydric alcohol esters. Ethylene glycol mono and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty esters, ethoxylated glyceryl monostearate, 1, 3-butylene glycol monostearate, 1, 3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters.

(4) Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate and arachidyl behenate.

(5) Sterol esters, of which cholesterol fatty acid esters are examples thereof.

Fatty acids having from 10 to 30 carbon atoms may also be included as cosmetically acceptable carriers for compositions of this invention. Illustrative of this category are pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidic, behenic and erucic acids.

Humectants of the polyhydric alcohol-type may also be employed as cosmetically acceptable carriers in compositions of this invention. The humectant aids in increasing the effectiveness of the emollient, reduces scaling, stimulates removal of built-up scale and improves skin feel. Typical polyhydric alcohols include glycerol, polyalkylene glycols and more preferably alkylene polyols and their derivatives, including propylene glycol, dipropylene glycol, polypropylene glycol, polyethylene glycol and derivatives thereof, sorbitol, hydroxypropyl sorbitol, hexylene glycol, 1,3-butylene glycol, 1,2,6-hexanetriol, ethoxylated glycerol, propoxylated glycerol and mixtures thereof. For best results the humectant is preferably propylene glycol or sodium hyaluronate. The amount of humectant may range anywhere from 0.5 to 30%, preferably between 1 and 15% by weight of the composition.

Thickeners may also be utilized as part of the cosmetically acceptable carrier of compositions according to the present invention. Typical thickeners include crosslinked acrylates (e.g. Carbopol 982), hydrophobically-modified acrylates (e.g. Carbopol 1382), cellulosic derivatives and natural gums. Among useful cellulosic derivatives are sodium carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose and hydroxymethyl cellulose. Natural gums suitable for the present invention include guar, xanthan, sclerotium, carrageenan, pectin and combinations of these gums. Amounts of the thickener may

range from 0.0001 to 5%, usually from 0.001 to 1%, optimally from 0.01 to 0.5% by weight.

Collectively the water, solvents, silicones, esters, fatty acids, humectants and/or thickeners will constitute the cosmetically acceptable carrier in amounts from 1 to 99.9%, preferably from 80 to 99% by weight.

Additional Optional Skin Benefit Materials:

An oil or oily material may be present, together with an emulsifier to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophilic-lipophilic balance (HLB) of the emulsifier employed.

Surfactants may also be present in cosmetic compositions of the present invention. Total concentration of the surfactant will range from 0.1 to 40%, preferably from 1 to 20%, optimally from 1 to 5% by weight of the composition. The surfactant may be selected from the group consisting of anionic, nonionic, cationic and amphoteric actives. Particularly preferred nonionic surfactants are those with a C10-C20 fatty alcohol or acid hydrophobe condensed with from 2 to 100 moles of ethylene oxide or propylene oxide per mole of hydrophobe; C2-C10 alkyl phenols condensed with from 2 to 20 moles of alkylene oxide; mono- and di- fatty acid esters of ethylene glycol; fatty acid monoglyceride; sorbitan, mono- and di- C8-C20 fatty acids; block copolymers (ethylene oxide/propylene oxide); and polyoxyethylene sorbitan as well as combinations thereof.

Alkyl polyglycosides and saccharide fatty amides (e.g. methyl gluconamides) are also suitable nonionic surfactants.

Preferred anionic surfactants include soap, alkyl ether sulfate and sulfonates, alkyl sulfates and sulfonates, alkylbenzene sulfonates, alkyl and dialkyl sulfosuccinates, C8-C20 acyl isethionates, acyl glutamates, C8-C20 alkyl ether phosphates and combinations thereof.

The preferred compositions include additional sunless tanning agents, tyrosine or N-alkyl eryosine derwatives such as DOPA, cysteinyl DOPA, dihydroxyindole, and/or basic peptides, such as poly-lysine or poly-arginine.

Physiologoc DNA fragments, such as those disclosed by US 5,470,577;US 5,532,001; US 5,580,547; US 5,643,556, incorporated by reference herein, may also be included. Such physiologic DNA fragments may provide competitive binding to stratum corneum/epidermal enzymes, thus increasing the stability of non-physiologic DNA fragment analogs.

The preferred compositions avoid the extremes of pH, in order to further improve the stability of non-physiologic DNA fragment analogs. The preferred compositions have a pH in the range of from 3.8 to 8, preferably from 5.5 to 7.5.

In order to enhance the delivery of the active ingredient through the skin, the composition may optionally be used in conjunction with a device known in the literature for enhancing delivery through the skin including but not

limited to occlusive patches, iontophoretic systems and sonic energy devices.

EXAMPLE 1

This example investigated the stability of thymidine dinucleotide (pTpT) in organ culture.

Freshly obtained pigmented pig skin was scrubbed thoroughly with bactericidal soap, and dermatomed to 0.2mm. Skin was then incubated for 30 minutes in Dulbecco's Modified Eagle's Medium (DMEM) containing 500µ/ml penicillin, 500µg/ml streptomycin and 2.5µg/ml Fungizone. Skin was removed dabbed dry with a sterile wipe and cut into $2cm^2$ pieces. 2% pTpT ($0.5mg/cm^2$) in PG/DMSO (25%/75%) or PG/DMSO alone (vehicle control) was applied evenly to the surface of the pig skin which was then placed epidermis up in Transwell plates (Costar) and maintained at 37^0C in culture. Culture medium was DMEM supplemented with L-Glutamine (2mM) + 100µ/ml penicillin, 100µ/ml streptomycin, 0.5µg/ml Fungizone. At various time interval after application (20 min. 1h, 3h, 6h and 24h), biopsies were harvested, rinsed in PBS to remove excess surface pTpT and then snap frozen at -80^0C overnight. Epidermis and stratum corneum were separated from the dermis by scraping with a scalpel and then extracted on ice with PBS + 0.1% Tween 20. After 30 minutes, samples were centifuged at 15,000xg and the soluble fraction (containing extracted pTpT) was analysed by HPLC (OD 260nm) to assess the pTpT content. The HPLC was previously calibrated with standards of pTpT as well as TpT, thymidine monophosphate (TMP) and

thymidine - the most likely breakdown products of pTpT. The results that were obtained are summarized in Table 1.

TABLE 1

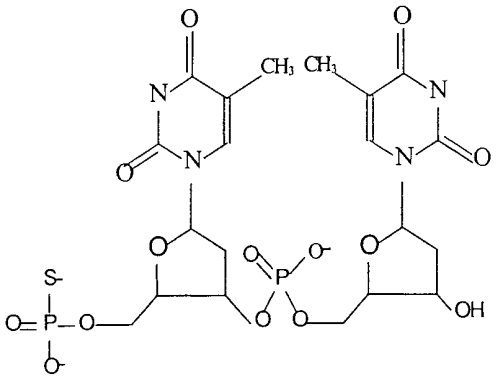
		HPLC Peak Areas (O.D. 260nm)	
Sample	Time elapsed after topical application	pTpT	Thymidine
Epidermis + Stratum Corneum	20 minutes	166765	0
Epidermis + Stratum Corneum	1 hour	162954	177245
Epidermis + Stratum Corneum	3 hours	211968	198353
Epidermis + Stratum Corneum	6 hours	111980	259310
Epidermis + Stratum Corneum	24 hours	0	0

It can be seen from the results in Table 1 that a major obstacle preventing delivery of these DNA fragments was their rapid degradation by skin enzymes.

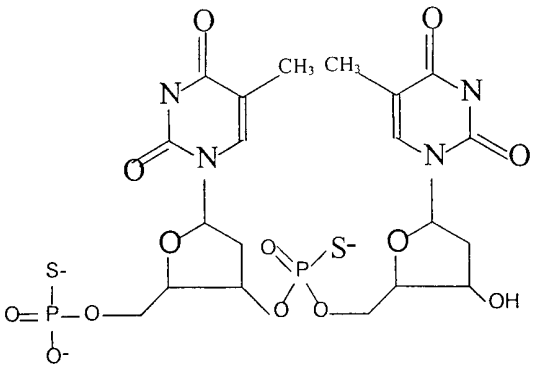
EXAMPLE 2

This example describes the preparation of some phosphorothioate analogs suitable for use in the present invention.

Compound 1: p(s)TpT (thymidine dinucleotide 5' phosphorothioate)



Compound 2: p(s)Tp(s)T (thymidine dinucleotide 5',3'-diphosphorothioate)



Phosphorothioate thymidine dinucleotides are prepared using standard automated solid phase synthesis using a commerically available synthesizer (1μM scale). Compound 1 is prepared from CPG supported DMTrO-dT loaded through a

succinyl linker. After 5' detritylation with 3% DCA in CH (90 sec), and washing with acetonitrile (30 sec), the support bound T nucleoside is reacted with 0.1M T-cyanoethyl phosphoramidite in acetonitrile in the presence of 0.5M tetrazole (30 sec). The bound phosphotriester is then oxidized for 50 seconds with 0.1M iodine in pyridine/ THF / water (20/80/2). After detritylation, the 5' OH group is phosphitilated with 150µl of 0.1M DMT-OCH2CH2SO2CH2CH2OP-(OCH2CH2CN)N(iPr)2 (Phosphate-CE - Cruachem) in CH3CN plus 150µl of 0.5M tetrazole in CH3CN. The resulting phosphite is sulphurized with Beaucage's reagent as previously described (Iyer et al., *J. Am. Chem. Soc., Vol. 112: 1253 (1990)* and *J. Org. Chem. 55: 4699*) and the DMT group cleaved with 3% DCA in CHCl2 (90 sec). The supported dinucleotide is then worked up in a conventional manner.

Compound 2 is prepared in a similar fashion to compound 1 except that instead of oxidizing with iodine, the initial phosphotriester is first reacted with Beaucage's reagent, detritylated, then 5' phosphorylated as described for compound 1, and further with the addition of a second sulfurization step after 5' phosphorylation using Beaucage's reagent.

EXAMPLE 3

This example describes the skin homogenate assay which determines whether a non-physiologic DNA fragment is sufficiently stable for use in the present invention. The example investigated the melanogenic activity of the non-physiologic DNA fragment analogs prepared in example 2.

Skin Homogenate Assay:

Freshly obtained piglet skin was shaved, washed with antimicrobial soap (Vionex, Viro Research Intl.), rinsed and then dermatomed to 400µm thickness. Approximately $10cm^2$ of the dernatomed skin was cut into small pieces with a scalpel and placed in a centrifuge tube, on ice with 2ml ice cold TBS. This was then homogenized extensively (5 min., 4^0C) with a hand-held 'Tissue Tearor' (Biospec Products Inc.) on the maximum setting until a fine slurry was formed. This was then centrifuged at 15000g (4^0C) for 10 minutes, the supernatant collected and the protein concentration of this supernatant determined using the BCA assay (Pierce). Homogenates were immediately frozen and stored at -20^0C until used in the assay.

Reactions were conducted in Microfuge tubes in a total volume of 100µl. The reaction buffer was prepared as follows:

TBS (pH7.0)	= 60µl
Skin homogenate, freshly thawed (5mg/ml)	= 20µl (total = 100µg protein)
Calcium chloride (20mM)	= 5µl (final = 1mM)
Magnesium chloride (20mM)	= 5µl (final = 1mM)
DNA analog (2mM)	= 10µl (final 0.2mM)
Total	100µl

Reactions were initiated by adding the homogenate to the analog in the TBS Ca/Mg buffer, vortexing, and placing the tube in a 37^0C oven. At the indicated time, reactions were stopped by addition of 11µl of 10X Stop solution:

10X stop solution:

500mM sodium fluoride
50mM EDTA
50mM L-tartaric acid.

After addition of the stop solution, samples were vortexed and immediately frozen prior to liquid chromatographic (LC) quantification of analog content.

Column: Phenomenex, Intersil OD2, 5 micron, 150x4.6 mm
Dectection: UV at 265 nm
Flow: 0.5 to 1.0 mL/min depending upon the analog

Mobile phase: 13.6 gm/L Potassium phosphate in water adjusted to pH 7-7.1(90%) and 10% Methanol.

Standards of each analog were prepared to determine specific retention times, and a thymidine standard (the major metabolite) was also used. Degradation rates were determined by following the decrease in peak height of the intact analogs with time.

The results that were obtained are summarized in Table 2. The results represent an average of two experiments.

TABLE 2

Test Compound	% Degraded after 30 mins.	% Degraded after 60 mins.	% Intact after 60 mins.
pTpT	5.8%	24.8%	75.2%
p(s)TpT	7.4%	14.8%	85.2%
p(s)Tp(s)T	<2%	<2%	>98%

It can be seen from the results in Table 2 that p(s)TpT and p(s)Tp(s)T were more than 80% intact, whereas the physiological fragment, pTpT, was not.

EXAMPLE 4

This example investigated the melanogenic activity of the non-physiologic DNA fragment analogs prepared in example 2.

Freshly obtained pigmented piglet skin was scrubbed thoroughly with bactericidal soap, and dermatomed to 0.2mm. Skin was then incubated for 30 minutes in Dulbecco's Modified Eagle's Medium (DMEM) containing 500µ/ml penicillin, 500µg/ml strptomycin and 2.5µg/ml Fungizone. 7mm diameter biopsies were them punched into and placed epidernis up, 3 per well in 6 well Transwell plates. (Costar) Biopsies were maintained at 37C, 5% CO^2 in serum-free DMEM supplemented with L-Glutamine (2mM) + 100µ/ml penicillin, 100µg/ml streptomycin, 0.5µg/ml Fungizone. On day 2, pTpT analogues dissolved in water were added to the appropriate wells at a final concentration in the media of 100µM. Control wells were treated with diluent (water) only. On day 4, the media was changed and fresh analogs added along with 0.2µCi/well of ^{14}C-labelled thiouracil to monitor melanin formation (Whittaker *J. Biol. Chem, 246, 6217-6226 (1971)*). On day 7, the biopsies were harvested, and to remove unincorporated thiouracil, were washed with 2M sodium bromide, 2 x 5% cold TCA and finally 1x cold PBS. Biopsies were then transferred to glass scintillation vials and incubated with 1N NaOH in an oven at 45^0C for o/n to solubilize the tissue and melanin. After neutralization with 1N HCl, radioactivity was quantified by scintillation counting. The averaged results of 15 biopsies for each treatment are summarized in Table 3 below.

TABLE 3

	Control (basal melanin formation)	pTpT	p(s)TpT	p(s)Tp(s)T
Mean ^{14}C-TU incorporation/ biopsy (n=15)	3788 ± 911	4530 ± 936	4806 ± 560	4387 ± 574
% of Control	100	120	127	116
p value vs. Control		0.0302	0.0007	0.0276

It can be seen from the results in Table 3 that each of the analogs increased melanogenesis above that of control biopsies, demonstrating that the pigmentary activity of these modified, nuclease-resistant dinucleotides is comparable to that of pTpT.

It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be made in the illustrated embodiments without departing from the invention as defined in the claims. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

CLAIMS

1. A cosmetic skin care composition comprising:
   (a) a non-physiologic DNA fragment which
   - remains at least 80% intact after one hour at 37°C in skin homogenate assay; and
   - increases melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay; and
   (b) a cosmetically acceptable vehicle.

2. The composition of claim 1, wherein the non-physiologic DNA fragment comprises at least two nucleotides and modified internucleotide linkage.

3. The composition of claim 1 wherein the non-physiologic DNA fragment is a phosphorothioate DNA analog.

4. The composition of claim 1 wherein the non-physiologic DNA fragment comprises a nucleotide with modified sugar.

5. The composition of claim 1 wherein the non-physiologic DNA fragment comprises less than 8 nucleotides.

6. A method for protecting human skin against ultraviolet damage comprising applying topically to the skin a non-physiologic DNA fragment which remains at least 80% intact after one hour at 37°C in skin homogenate assay; and increases melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay.

7. A method for stimulating pigmentation of human skin comprising applying topically to the skin a non-physiologic DNA fragment which remains at least 80% intact after one hour at 37°C in skin homogenate assay; and increases melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay.

8. A cosmetic self-tanning and/or anti-aging product comprising:

(i) a package;

(ii) composition contained within a package and comprising, in a cosmetically acceptable vehicle, a non-physiologic DNA fragment analog which which remains at least 80% intact after one hour at 37°C in skin homogenate assay, and increases melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay; and

(iii) written instructions to use the composition to obtain tanning of the skin in the absence of sun exposure.

9. A self-tanning and/or anti-aging product comprising:

(i) a device;

(ii) composition packaged along with the device and comprising, in a cosmetically acceptable vehicle, a non-physiologic DNA fragment analog which which remains at least 80% intact after one hour at 37°C in skin homogenate assay, and increases melanin production in melanocytes by at least 10%, as determined by in vitro melanogenesis assay; and

(iii) written instructions to use the composition with the device to obtain tanning of the skin in the absence of sun exposure.

10. Use of a composition according to any one of Claims 1 to 5 for the preparation of a composition for protecting human skin against ultraviolet radiation damage.

11. Use of a composition according to any one of Claims 1 to 5 for the preparation of a composition for stimulating pigmentation of human skin.