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(54) **METHODS AND COMPOSITIONS FOR TREATING KERATIN HYPERPROLIFERATIVE DISORDERS**

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(57) **ABSTRACT**

A method for keratin hyperproliferation disorders such as corns, calluses, or keratosis pilaris (KP) by administering to a subject experiencing the disorder a therapeutically effective amount of an RNA sequence which inhibits expression of a gene encoding for a keratin selected from the group consisting of K6a, K6b, K16, K17, and combinations thereof.

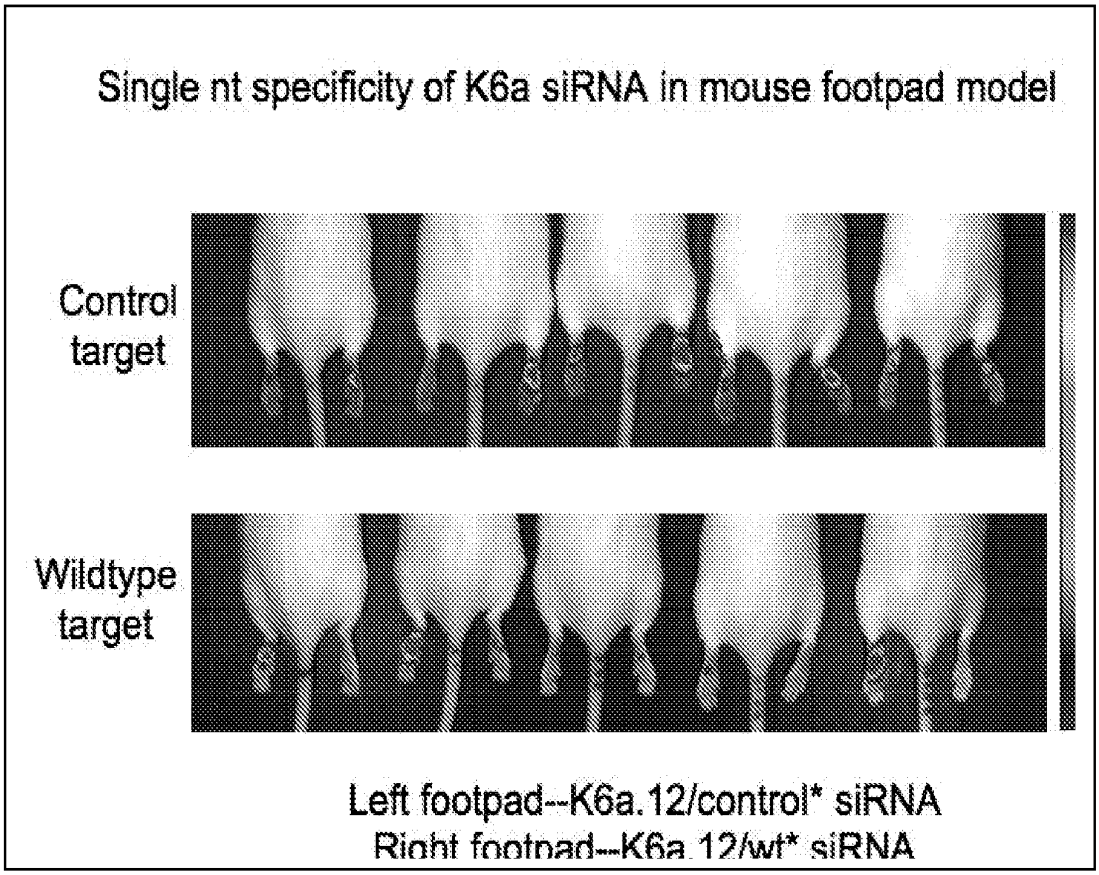


FIGURE 1A

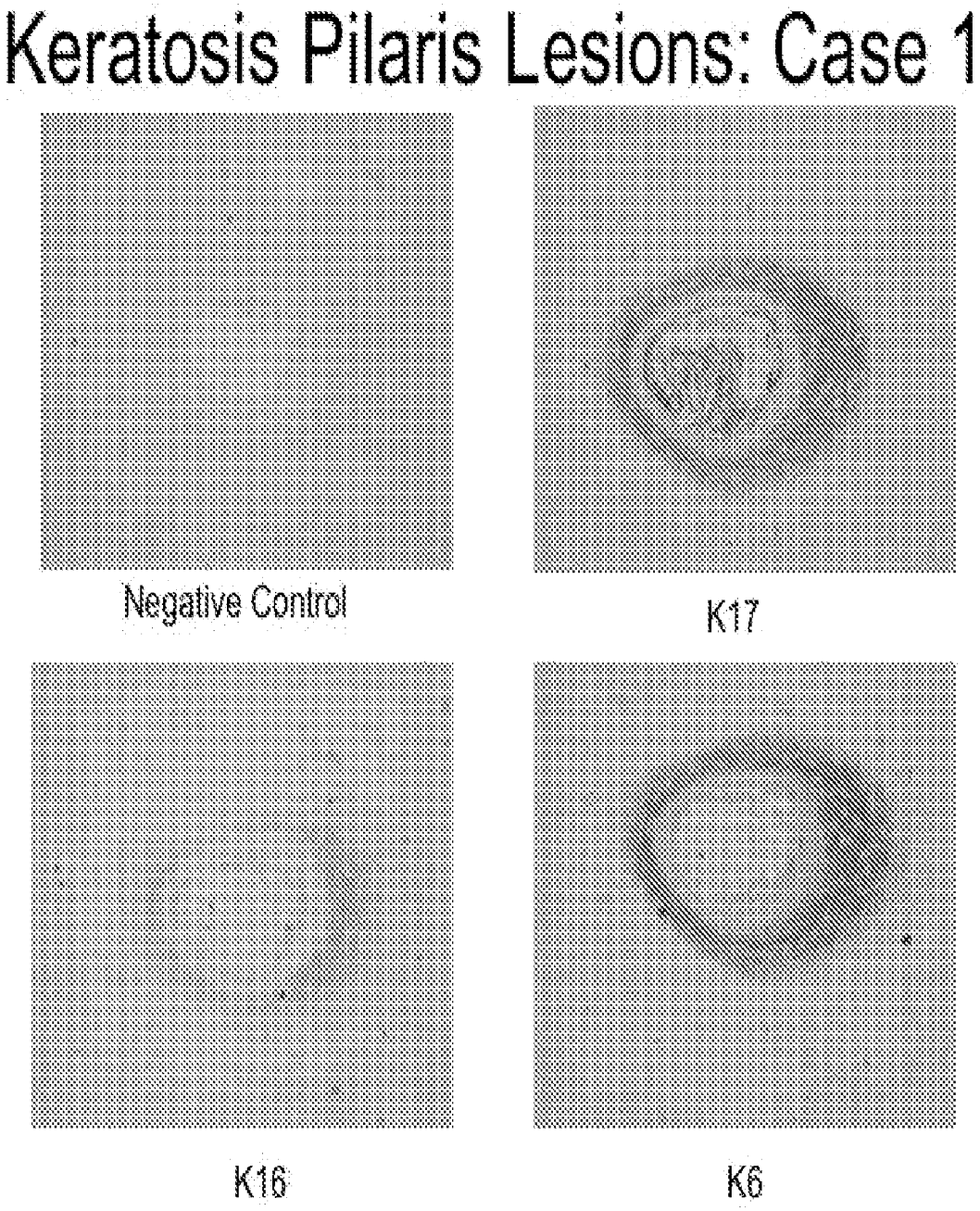

Keratosis Pilaris Lesions: Case 1
Negative Control
K17
K16
K6

FIGURE 1B

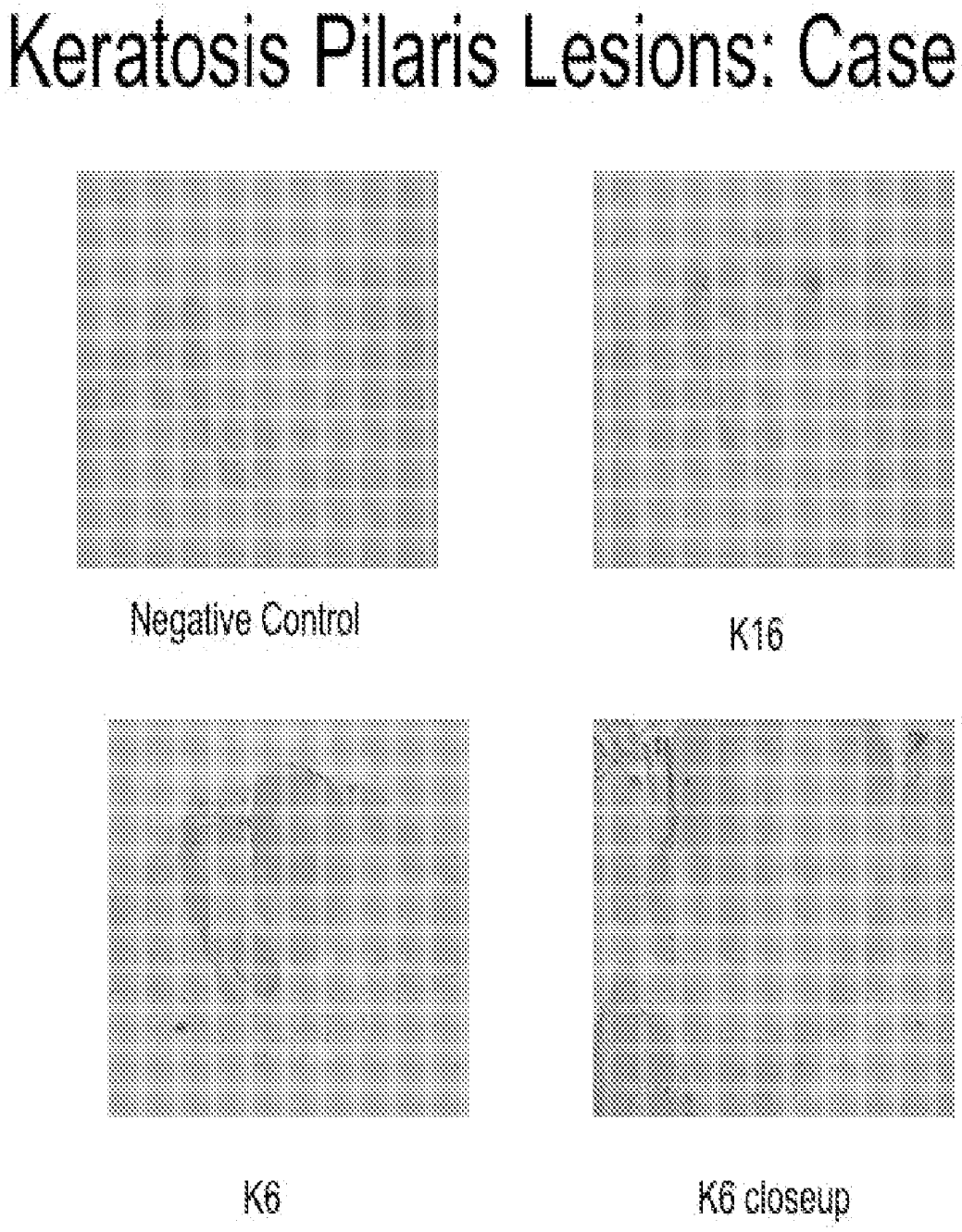

Keratosis Pilaris Lesions: Case 2
Negative Control
K16
K6
K6 closeup

FIGURE 1C

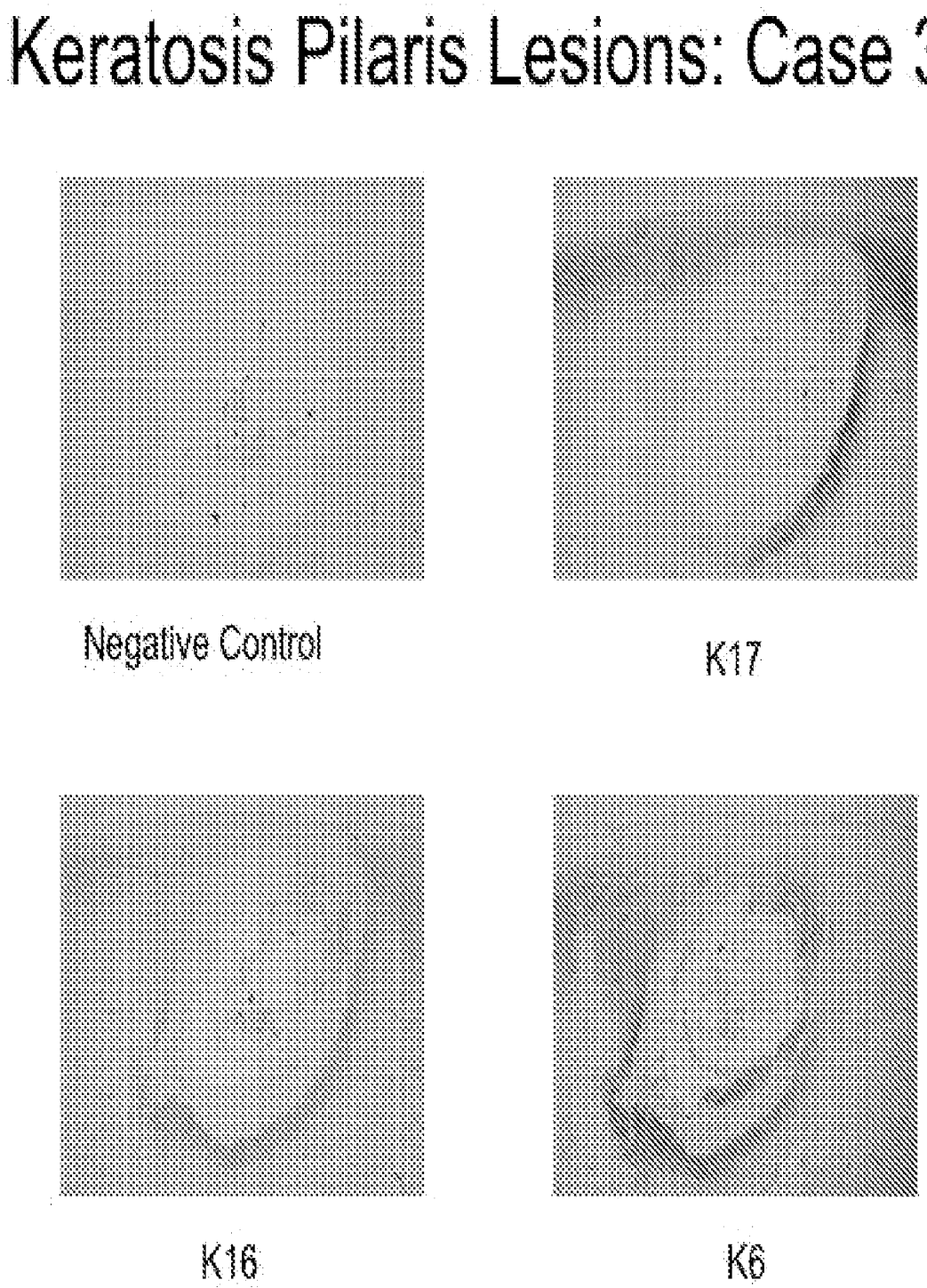

Keratosis Pilaris Lesions: Case 3
Negative Control
K17
K16
K6

FIGURE 1D

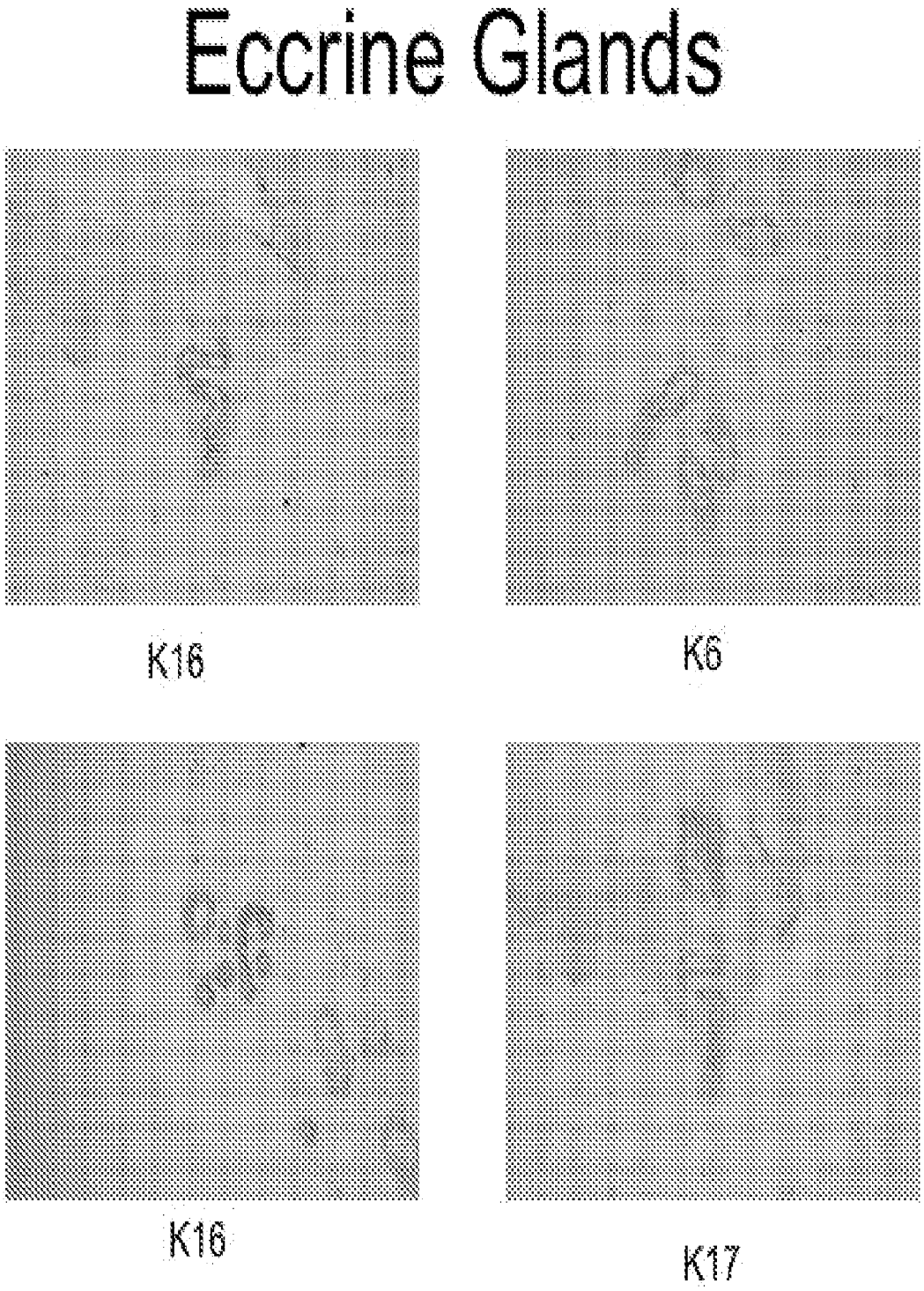


FIGURE 2

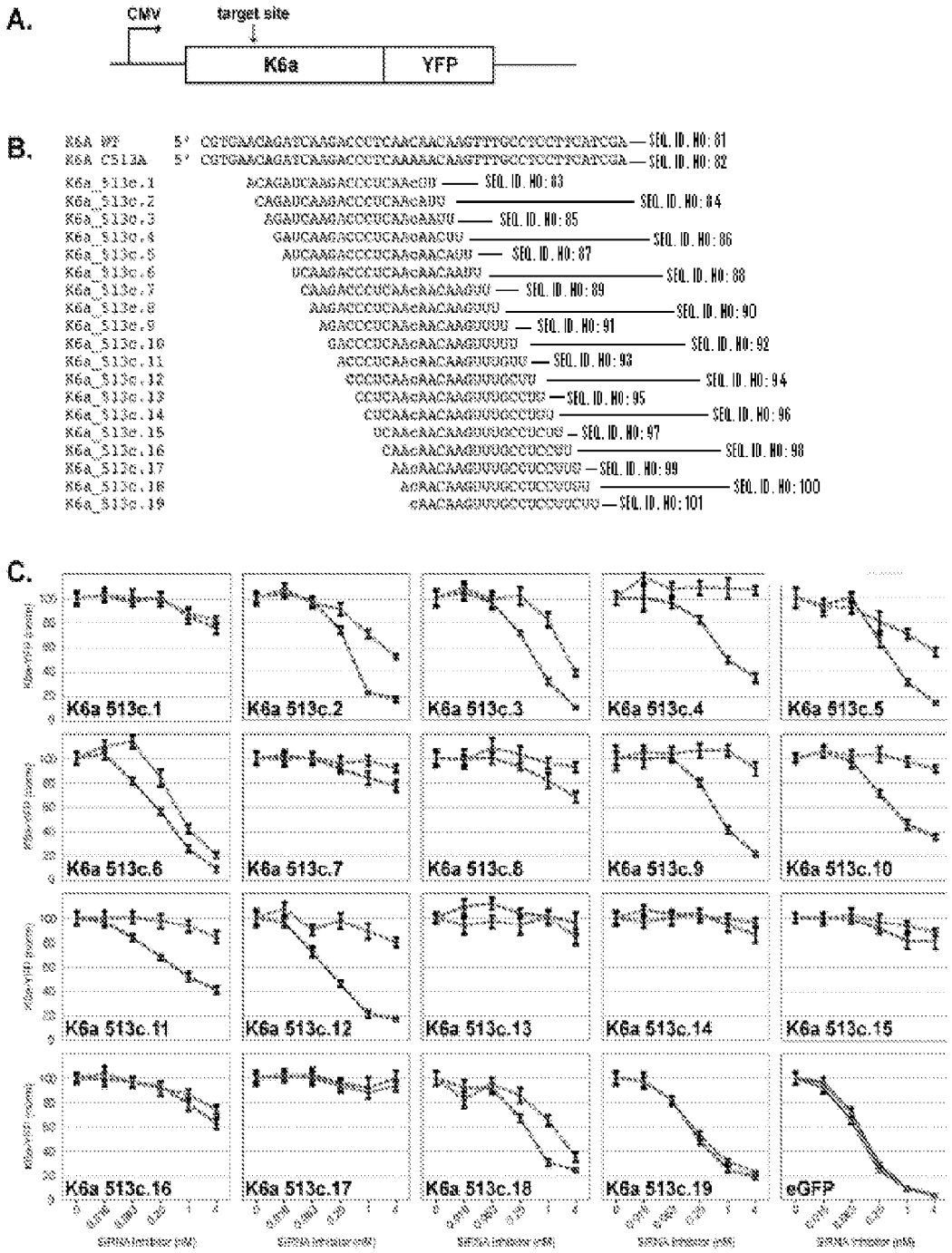

A.
CMV
target site
K6a
YFP
B.
K6A WT 5' CGTGAACAGATCAAGACCGTCAACAACAAGTTTGCCTCCTTCAACGA — SEQ. ID. NO: 81
K6A C513A 5' CGTGAACAGATCAAGACCGTCAAAAACAAGTTTGCCTCCTTCAACGA — SEQ. ID. NO: 82
K6a_513c.1 ACAGATCAAGACCGTCAAcGU — SEQ. ID. NO: 83
K6a_513c.2 CAGATCAAGACCGTCAACAUU — SEQ. ID. NO: 84
K6a_513c.3 AGATCAAGACCGTCAAcAAUU — SEQ. ID. NO: 85
K6a_513c.4 GATCAAGACCGTCAAcAACUU — SEQ. ID. NO: 86
K6a_513c.5 ATCAAGACCGTCAAcAACAGU — SEQ. ID. NO: 87
K6a_513c.6 TCAAGACCGTCAAcAACAAUU — SEQ. ID. NO: 88
K6a_513c.7 CAAGACCGTCAAcAACAAGUU — SEQ. ID. NO: 89
K6a_513c.8 AAGACCGTCAAcAACAAGUUU — SEQ. ID. NO: 90
K6a_513c.9 AGACCGTCAAcAACAAGUUUU — SEQ. ID. NO: 91
K6a_513c.10 GACCGTCAAcAACAAGUUUUU — SEQ. ID. NO: 92
K6a_513c.11 ACCGTCAAcAACAAGUUUGUU — SEQ. ID. NO: 93
K6a_513c.12 CCGTCAAcAACAAGUUUGCUU — SEQ. ID. NO: 94
K6a_513c.13 CGTCAAcAACAAGUUUGCCUU — SEQ. ID. NO: 95
K6a_513c.14 GTCAAcAACAAGUUUGCCUCU — SEQ. ID. NO: 96
K6a_513c.15 TCAAcAACAAGUUUGCCUCCU — SEQ. ID. NO: 97
K6a_513c.16 CAAcAACAAGUUUGCCUCCUU — SEQ. ID. NO: 98
K6a_513c.17 AAcAACAAGUUUGCCUCCUUU — SEQ. ID. NO: 99
K6a_513c.18 AcAACAAGUUUGCCUCCUUCU — SEQ. ID. NO: 100
K6a_513c.19 cAACAAGUUUGCCUCCUUCUU — SEQ. ID. NO: 101
C.
K6a 513c.1
K6a 513c.2
K6a 513c.3
K6a 513c.4
K6a 513c.5
K6a 513c.6
K6a 513c.7
K6a 513c.8
K6a 513c.9
K6a 513c.10
K6a 513c.11
K6a 513c.12
K6a 513c.13
K6a 513c.14
K6a 513c.15
K6a 513c.16
K6a 513c.17
K6a 513c.18
K6a 513c.19
eGFP

FIGURE 3

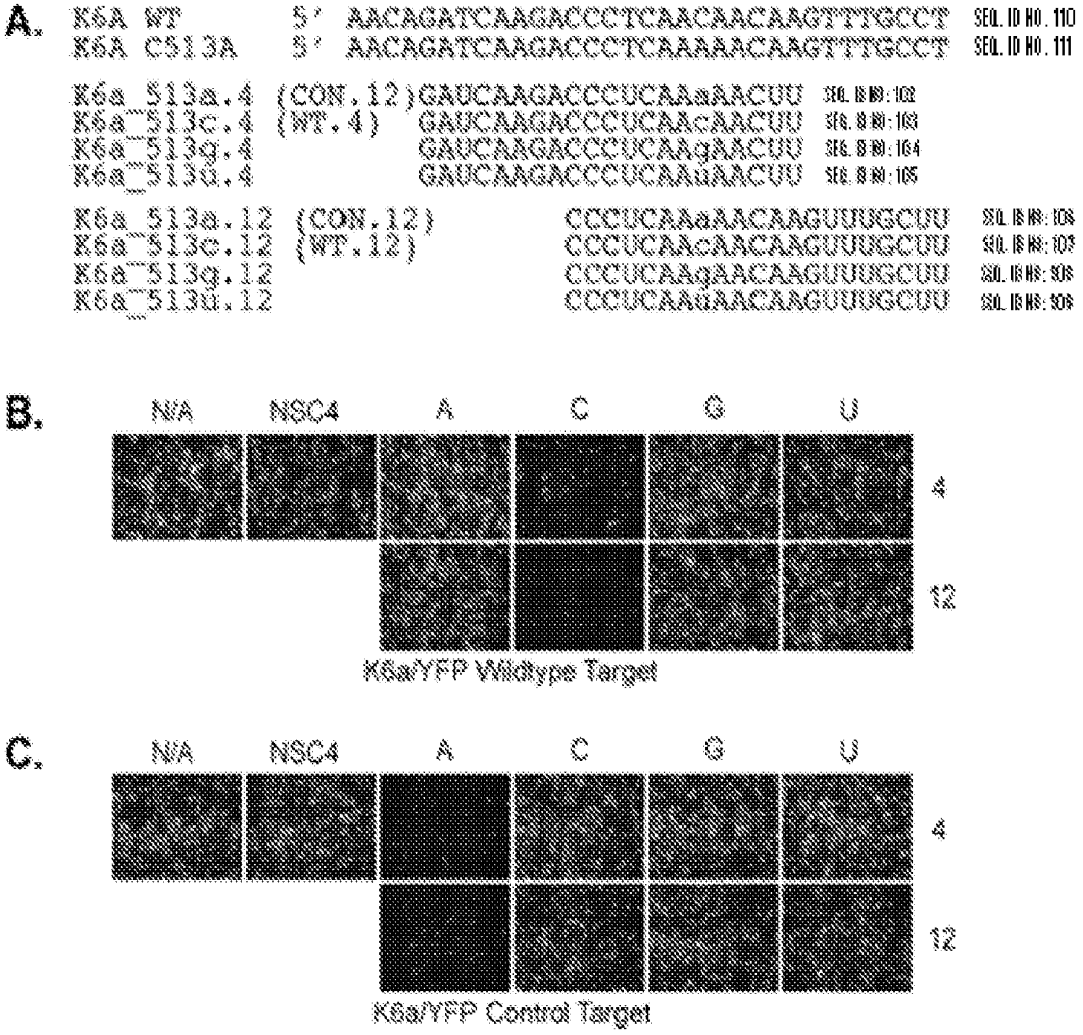

A.
K6A WT 5' AACAGATCAAGACCCTCAACAACAAGTTTGCCT SEQ ID NO. 110
K6A C513A 5' AACAGATCAAGACCCTCAAAAACAAGTTTGCCT SEQ ID NO. 111
K6a_513a.4 (CON.12)GAUCAAGACCCUCAAaAACUU SEQ ID NO: 102
K6a_513c.4 (WT.4) GAUCAAGACCCUCAAcAACUU SEQ ID NO: 103
K6a_513g.4 GAUCAAGACCCUCAAgAACUU SEQ ID NO: 104
K6a_513u.4 GAUCAAGACCCUCAAuAACUU SEQ ID NO: 105
K6a_513a.12 (CON.12) CCCUCAAaAACAAGUUUGCUU SEQ ID NO: 106
K6a_513c.12 (WT.12) CCCUCAAcAACAAGUUUGCUU SEQ ID NO: 107
K6a_513g.12 CCCUCAAgAACAAGUUUGCUU SEQ ID NO: 108
K6a_513u.12 CCCUCAAuAACAAGUUUGCUU SEQ ID NO: 109
B.
N/A
NSC4
A
C
G
U
4
12
K6a/YFP Wildtype Target
C.
N/A
NSC4
A
C
G
U
4
12
K6a/YFP Control Target

FIGURE 4

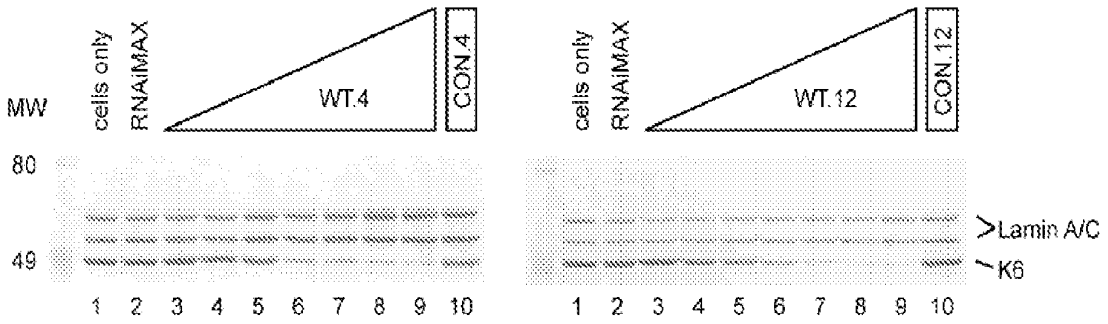
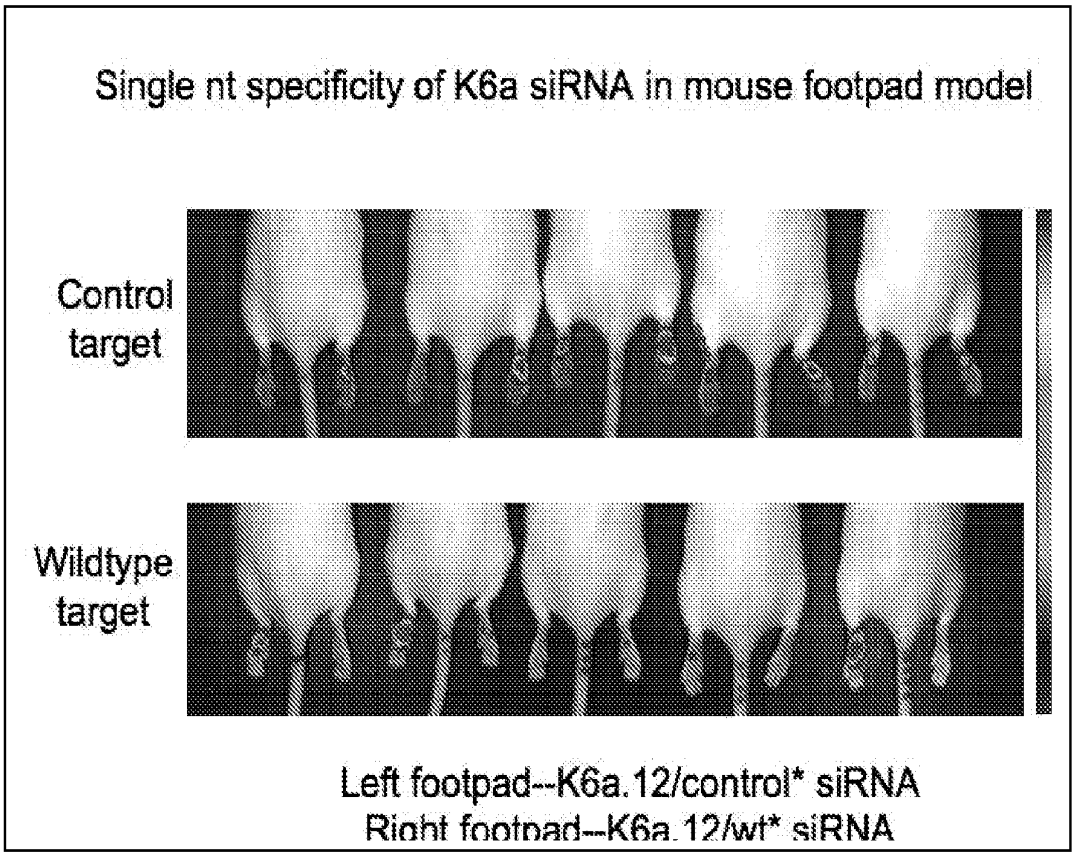

MW
cells only
RNAiMAX
WT.4
CON.4
cells only
RNAiMAX
WT.12
CON.12
80
49
Lamin A/C
K6
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10

FIGURE 5


Single nt specificity of K6a siRNA in mouse footpad model
Control target
Wildtype target
Left footpad--K6a.12/control* siRNA
Right footpad--K6a.12/wt* siRNA

METHODS AND COMPOSITIONS FOR TREATING KERATIN HYPERPROLIFERATIVE DISORDERS

FIELD OF THE INVENTION

[0001] The present invention is related generally to methods and compositions for treating cutaneous disorders of epidermal hyperproliferation including: calluses, corns, keratosis pilaris (KP), psoriasis, and other less common conditions such as keratosis follicularis, pityriasis rubra pilaris, Clouston syndrome, and other palmoplantar keratodermas. More particularly, the present invention is related to the use of RNAi and in particular transdermally-administered siRNA or shRNA to treat calluses, corns (clavi) and KP.

BACKGROUND OF THE INVENTION

[0002] Disorders that result in hyperproliferation of the epidermis such as corns, calluses, keratosis pilaris, psoriasis, and other less common conditions, account for a large percentage of skin disease worldwide. A commonality among these disorders is that friction and/or pressure typically precipitate or worsen the clinical manifestations of the disease. The shared molecular feature among these disorders of hyperproliferation is expression of a panel of keratins (the hyperproliferation keratins, K6, K16, and K17).

[0003] Keratosis pilaris is a very common, benign skin condition in which keratin protein in the skin forms hard plugs within hair follicles and often lessens or disappears with age. KP consists of a clustering of small, usually 1-2 mm, flesh-colored to slightly erythematous follicular bumps commonly found on the backs of the upper arms. The texture is frequently very coarse due to protrusion of the keratin plugs from the hair follicles. KP may also appear on the buttocks and thighs, where it may be precipitated or worsened by friction from clothing. Less commonly, KP can be seen on the face, where it is termed KP atrophicans faciei. Histologically, these lesions demonstrate keratin plugging of the hair follicles. The condition is generally worse in winter and may improve in the summer. It is associated with atopic dermatitis (eczema) and is hereditary, but the genetic basis of the disease is unknown.

[0004] Indeed, the underlying genetic cause of corns, calluses, and psoriasis also remains unknown, but they are similarly caused by friction and pressure generated between the foot and footwear. Histologically, these lesions show a thickened stratum corneum and over time, they develop a central keratin plug that presses painfully into the dermis. The shared pathophysiology involved in the development of corns, calluses, and KP lesions likely explains the shared overexpression of the hyperproliferative keratins.

[0005] Psoriasis, although not considered to be a classic disorder of keratinization, also shows overexpression of the hyperproliferative keratins, primarily K16 and K17. In addition, psoriatic lesions tend to develop or extend into areas of trauma, where these same keratins are activated (a symptom referred to as Koebnerization).

[0006] Although good emollients or topical treatment with keratolytic agents such as urea, lactic acid, Retin A (tretinoin), or vitamin D analogs may soften and soothe the symptoms of epidermal proliferation, there is currently no medication that eliminates the disease manifestations. Available treatments are directed at symptomatic manifestations of the disorders but generally do not affect the underlying cause as it has heretofore been unknown. As individual patients are generally troubled by different manifestations of the disease, no single treatment plan is known to be effective for treating the hyperproliferation as a whole. Treatment options for epidermal hyperproliferation fall into several broad categories, non-invasive (mechanical), invasive (surgical), chemical, and pharmacological. Currently no treatment options are available for corns, calluses or KP, which address the underlying cause of the disorder and therefore prevent the occurrence of symptoms.

SUMMARY OF THE INVENTION

[0007] As such it would be advantageous to develop a method of treatment for corns, calluses, and/or KP, which prevented or suppressed the occurrence of the symptoms. The present invention provides methods and compositions for treating or preventing the manifestation of disorders of keratin hyperproliferation, including primarily corns, calluses, psoriasis and keratosis pilaris. In one embodiment a method of treating or preventing hyperproliferation skin disorders includes administering a therapeutically effective amount of an RNA sequence which inhibits expression of a gene encoding for a keratin selected from the group consisting of K6a, K6b, K16, K17, and combinations thereof.

[0008] In addition to the foregoing, the present invention encompasses formulations for administering the RNA sequences recited herein to target cells of a subject. Examples of such formulations include without limitation, topical formulations, including gels, lotions, crèmes, ointments, adhesives, and pastes, as well as transdermal patches, intradermal injections (including needle arrays and "dissolvable" needles), iontophoretic mechanisms, electroporation, sonophoresis, etc.

[0009] Reference will now be made to the exemplary embodiments of the present invention, and specific language will be used herein to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. **1** shows comparative histology and immunostaining for keratins including K6, K16 and K17 from patient KP biopsies as well as biopsies from eccrine glands as controls (FIG. **1**D). The immunostained KP sections show strong expression of the "inducible keratins" including K6, K16 and K17. Three separate patient biopsies of KP on the upper outer arms are shown (FIG. **1**A, FIG. **1**B, and FIG. **1**C). Each of these lesions demonstrates the typical keratin plugging of the follicular structures. Immunostaining with anti-K6, -K16, and -K17 shows expression of the hyperproliferative keratins relative to a negative control. Normal follicular structures do not typically demonstrate this level of hyperproliferative keratin expression.

[0011] FIG. **2** shows a sequence walk of siRNA inhibitors targeting a specific region of the K6a mRNA (i.e. the region surrounding C513). The fusion bicistronic reporter system is shown in Panel A. Panel B shows the quantitative FACS results of a complete siRNA sequence walk of this specific region of K6a. SiRNAs (19+2 format) were designed and synthesized to screen all possible target sequences containing C513. Each siRNA was co-transfected into 293FT tissue culture cells with either a expression vector encoding a perfectly matched K6a(WT)/YFP fusion target mRNA, or a con-

trol mRNA (K6a(control)/YFP) which contains a single nucleotide change (C513A) to demonstrate single-nucleotide specificity (red). 48 hours following transfection, the cells were trypsinized and analyzed for YFP expression using a Becton Dickinson FACScan using channel FL1 (530 nm emission filter). 5,000 cells per transfection were analyzed. The data were generated by gating the cells and determining the percentage of cells that dropped below the gate with and without siRNA treatment. The data were normalized (to 100) and then corrected against cells transfected with NSC4 siRNA (non-specific control from Dharmacon). These results indicate that some siRNAs such as K6a 513c.4 (WT.4) and K6a 513c.12 (WT.12) can strongly discriminate between wildtype K6a and a control K6a that contains a single nucleotide mutation whereas other siRNAs such as K6a 513c.13-17 (WT.13-17) have little or no effect on either.

[0012] FIG. **3** shows that exact sequence identity is necessary for inhibition of wild type and control K6a expression by siRNAs at positions 4 and 12. A. SiRNAs corresponding to positions 4 and 12 were designed and synthesized to target all possible nucleotides at mRNA position 513. Each siRNA (1 nM final concentration) was co-transfected into 293FT tissue culture cells with 150 ng of either the K6a(WT)/YFP (Panel B) or K6a(control)/YFP (Panel C) expression plasmid and were visualized by fluorescence microscopy using an eGFP filter set. Only the siRNAs with exact sequence identity (WT siRNAs against the WT plasmid and control siRNAs against the control plasmid) showed inhibition of expression, while little or no effect was observed with the non-identical siRNAs, which differ only at nucleotide 513.

[0013] FIG. **4** shows inhibition of endogenous K6 expression in human HaCaT keratinocytes. HaCaT cells were transfected with increasing concentrations of wildtype-specific siRNAs (lanes 3-9 containing 0, 1, 2, 5, 10, 15 and 20 nM WT.4 or WT.12) and as controls 20 nM siRNA that target the single nucleotide change (C513A) (lane 10, CON.4 or CON.12). After 96 hrs, cells were harvested and lysed in SDS-PAGE loading buffer and subjected to denaturing SDS-PAGE analysis and electroblotted to nitrocellulose. K6 expression was detected by specific K6 antibody (Progen) and visualized by the NBT/BCIP system (Promega). The blot was subsequently reacted with an antibody specific to Lamin A/C (Upstate) to show equal lane loading and absence of generalized inhibition resulting from siRNA treatment. These results show that endogenous K6 can be potently down-regulated by siRNAs that also exhibit single-nucleotide specificity.

[0014] FIG. **5** shows inhibition of K6a(wildtype)/fLuc gene expression by specific siRNAs in a mouse footpad skin model. A. Mice (5 per group) were co-injected intradermally with ~10 μg K6a(WT)/fLuc (bottom mouse panel) or K6a (control)/fLuc (top mouse panel) expression plasmid and ~10 μg of either stabilized (siSTABLE™ from Dharmacon) WT.12 siRNA (right paw) or CON.12 siRNA (left paw). After 24 hrs, luciferase expression in the footpads was determined following IP luciferin injection by whole animal imaging using the Xenogen IVIS in vivo imaging system. Red color represents highest luciferase expression, purple lowest. These results show that the WT.12 siRNA can specifically block expression of wildtype K6a expression in a mouse system with little effect on a control target that only differs by a single nucleotide.

DETAILED DESCRIPTION OF THE INVENTION

[0015] A new genetic disorder therapy, which is being heavily researched is RNA interference (RNAi). RNAi is an evolutionarily conserved mechanism that results in specific gene inhibition. In the RNAi pathway, double-stranded RNA can effectively induce potent gene silencing without inducing an immune response. RNAi is mediated by RNA-induced silencing complex (RISC), a sequence specific, multi-component nuclease that destroys messenger RNAs homologous to the silencing trigger. RISC is known to contain short RNAs (from 15-31 nucleotides in length), which are derived from double-stranded RNA triggers. A more detailed discussion of the RNAi process in general may be found in *Gene Silencing by RNA Interference: Technology and Application* (Muhammad Sohail ed., 2005), which is incorporated herein by reference.

[0016] The present invention illustrates that diseases of the skin with well-described mechanisms are amenable to nucleic acid-based therapies. Although normal skin (and especially the stratum corneum) represents a formidable barrier to topical nucleic acid delivery, a number of methods have been used to successfully deliver nucleic acids to skin. The present invention uses a variety of delivery mechanisms to deliver key RNA inhibitors including intradermal injection and cream formulations.

[0017] Although the present invention illustrates the use of RNAi to treat KP, corns or calluses, the ability to locally deliver specific robust siRNA-based gene inhibitors would be a boon to patients suffering from a number of hair follicle skin disorders in addition to KP such as keratosis follicularis, and as such, the general principles embodied herein may be applied for treatment of such conditions.

[0018] Before particular embodiments of the present invention are disclosed and described, it is to be understood that this invention is not limited to the particular process and materials disclosed herein as such may vary to some degree. It is also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and is not intended to be limiting.

[0019] In describing and claiming the present invention, the following terminology will be used.

[0020] The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an RNA sequence" includes reference to one or more of such RNA sequences, and reference to "the genetic mutation" includes reference to one or more of such genetic mutation.

[0021] As used herein, "subject" refers to a mammal having who currently manifests, has in the past manifested, or is genetically predisposed to the potential manifestation of a hyperkeratotic skin (i.e. keratin hyperproliferation) condition or disorder. In some aspects, such subject may be a human.

[0022] The term "gene" refers to a nucleic acid comprising an open reading frame encoding a polypeptide.

[0023] The term "sequence" when used with respect to RNA inhibitors refers to at a minimum, a single strand oligonucleotide of between about 15 and 31 base pairs (siRNA), which may hybridize with target mRNA and thereby inhibits the expression of the targeted gene. The sequence may be formed and delivered to a subject as double stranded RNA, the second strand being complimentary to the inhibitory sequence, or as small hairpin RNA (shRNA), the inhibitory sequence being attached through a loop sequence to a sequence complimentary to the inhibitory sequence. The sequence may also include 2 nucleotide overhangs.

[0024] As used herein, the terms "target cell" or "target cells", refer to cells that produce keratin proteins, the

improper production of which contribute to a keratin hyperproliferation disorder. Such keratins include without limitation, those recited herein.

[0025] As used herein, the term "inhibition of" or "silencing of" with respect to genetic expression refers to the absence of, or at least an observable decrease in, the level of protein from a target gene.

[0026] As used herein, the term "hyperproliferation skin disorder" refers to disorders of the skin in which there is a hyperproliferation of the keratins K6 (K6a and/or K6b), K16, and/or K17. The hyperproliferation of the keratins can be from caused by any source including but not limited to external factors (e.g. rubbing or pressure of a shoe to form a callus or corn) or internal/biological factors (e.g. over expression of a gene).

[0027] The term "expression" with respect to a gene sequence refers to transcription of the gene and, as appropriate, translation of the resulting mRNA transcript to a protein.

[0028] "Specificity" refers to the ability to inhibit the target gene without manifest effects on other genes of the cell. The consequences of inhibition can be confirmed by examination of the outward properties of the cell or organism or by biochemical techniques such as RNA solution hybridization, nuclease protection, Northern hybridization, reverse transcription, gene expression monitoring with a microarray, antibody binding, enzyme linked immunosorbent assay (ELISA), Western blotting, radioimmunoassay (RIA), other immunoassays, and flow cytometry (FACS). For RNA-mediated inhibition in a whole organism or cell line, gene expression is conveniently assayed by use of a reporter or drug resistance gene whose protein product is easily assayed. Such reporter genes can include but are not limited to beta galactosidase (LACZ), beta glucoronidase (GUS), chloramphenicol acetyltransferase (CAT), green fluorescent protein (GFP) or other fluorescent proteins (e.g. YFP, BFP, CFP, DsRed, Tomato, etc.), horseradish peroxidase (HRP), luciferase (LUC), etc.

[0029] As used herein, "effective amount" or "therapeutically effective amount" of an RNA refers to a sufficient amount of RNA to perform an intended task and achieve an intended result. For example, an effective amount of siRNA may be an amount which is sufficient to silence expression a keratin gene. It is understood that various biological factors may affect the ability of a particular RNA sequence to perform its intended task. Therefore, an "effective amount" or a "therapeutically effective amount" may be dependent in some instances on such biological factors. Further, while the achievement of therapeutic effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic effects a somewhat subjective decision. The determination of an effective amount is well within the ordinary skill in the art of pharmaceutical sciences and medicine.

[0030] As used herein, the term "about" is used to provide flexibility to a numerical range endpoint by providing that a given value may be "a little above" or "a little below" the endpoint.

[0031] As used herein, the term "substantially" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result.

[0032] As used herein, sequences, compounds, formulations, delivery mechanisms, or other items may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

[0033] Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 0.5 to 10 g" should be interpreted to include not only the explicitly recited values of about 0.5 g to about 10.0 g, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 2, 5, and 7, and sub-ranges such as from 2 to 8, 4 to 6, etc. This same principle applies to ranges reciting only one numerical value. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

[0034] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. Although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, representative methods, devices, and materials are described below.

[0035] As mentioned above, keratosis pilaris is generally a disorder resulting in keratin plugging of hair follicles, and corns and calluses represent a reactive hyperproliferation in response to trauma. Although some of the manifestations of the disease differ by the location of the hyperproliferation (palms and soles versus perifollicular) the general underlying cause of each disorder is generally the same, overexpression of inducible keratin encoding genes. Keratins are the type I and type II intermediate filament proteins, which form a cytoskeletal network within all epithelial cells. Overexpression of these genes is associated with thickened, and abnormally cornified and frequently hyperproliferative epidermis which present clinically as a variety of conditions such as corns, calluses, KP and keratodermas such as PC. The overexpression of four keratin genes may be associated with corns, calluses, and KP, namely K6a, K6b, K16, and K17. The reason for overexpression of these genes is not known, but may involve trauma to the hands or feet or undesirable stimulation of the hair follicles by friction or other manipulation.

[0036] The present invention provides methods for treating corns, calluses and KP by administering therapeutically effective amounts of siRNAs that specifically target K6a, K6b, K16 and/or K17 in the subject. The prepared inhibitory sequences can vary in length but generally are from about 15 to 31 bases in length. These prepared sequences are generally considered to be small interfering siRNA (siRNA). The RNA sequences of the present invention can include modifications to either the phosphate-sugar backbone or the base. For example, the phosphodiester linkages of the RNA may be modified to include at least one of a nitrogen or sulfur or other heteroatom. Likewise, bases may be modified to block the activity of nucleases. The RNA sequence may be produced enzymatically or by partial/total organic synthesis; any modi-

fied ribonucleotide can be introduced by in vitro enzymatic or organic synthesis. The RNA sequences of the present invention can be administered as hybridized double stranded complementary RNA (dsRNA), as short single-stranded hybridized RNAs (typically siRNA), or alternatively as a single hairpin molecule of RNA (shRNA) that contains a 15 to 31-basepair stem. The desirability of using dsRNA vs. shRNA can vary depending on the particular sequence and the mutation for which inhibition is sought; however, both forms have been shown to be capable and effective for use in gene silencing. For more information on small hairpin RNA see Wang et al., *Molecular Therapy*, Vol. 12, No. 3, September 2005, which is hereby incorporated by reference in its entirety. Whether administered as dsRNA or shRNA, there are a variety of means by which the RNA sequences of the present invention can be delivered to a subject. Suitable delivery mechanisms include but are not limited to injection, including intradermal injection using single needles and needle arrays, topical formulations, such as lotions, creams, gels, ointments, jellies (such as petroleum jelly), adhesives, pastes, liquids, soaps, shampoos, transdermal patches, films, electrophoresis, or combinations thereof. In one aspect, the specific carrier utilized in the production of a formulation may be selected because of its positive impact on skin. For example, carriers that moisturize, hydrate, or otherwise benefit the skin can be used.

[0037] In some aspects, the RNA sequences of the present invention can be administered in combination with other therapeutically effective compounds. Ideally, such compounds would be those agents having a therapeutic skin effect, particularly on the manifestations of the disorder being treated. Examples of such compounds include but are not limited to corticosteroidsm, (e.g. hydrocortisone, prednisone, clobetasol propionate, etc.), a lanolin-containing product, aloe vera, urea, propylene glycol, α-hydroxy acids, lactic acid, salicylic acid, vitamin D_3 and its derivatives, vitamin A and retinoids, levothyroxin, NSAIDS, cyclosporine, methotrexate sodium, anthralin, acitretin, tazarotene, coal tar, clobetasol propionate, botulinum toxin, topical anesthetics, antihistamine, and combinations thereof.

[0038] Effectiveness of the KP inhibition can depend on the particular RNA inhibitor as well as the amount of inhibiting RNA administered to the subject. Other biologically related factors may also be variables in determining the effectiveness of the inhibitors. Therapeutically effective amounts of RNA sequences can be from about 0.1 mg to about 10 mg.

[0039] In one embodiment, the present invention provides a method of treating a subject with corns, calluses, and/or KP by administering to the subject an RNA sequence which inhibits the expression of the gene encoding for a keratin selected from the group of K6a, K6b, K16, K17, and combinations thereof. It has been discovered that there is redundancy of keratin expression in keratinocytes, and as such it is possible to suppress expression of wildtype keratins without causing unwanted side-effects. In other words, by simply eliminating production of any one or more of the above-recited keratins it may be possible to reduce or eliminate the symptoms of corns, calluses, and/or KP without any unwanted side effects because other keratins overlap the functions performed by the above-recited keratins. Additionally, due to the relatively small numbers of genes expressed in skin, it is believed that the methods of the present invention can be used effectively with minimal off-target effects.

[0040] Non-limiting examples of sequences which can be used to inhibit the expression of the K6a keratin include but are not limited to SEQ. TD NO: 1, SEQ. ID NO: 2, SEQ. ID NO: 3, SEQ. ID NO: 4, SEQ. ID NO: 5, SEQ. ID NO: 6, SEQ. ID NO: 7, SEQ. ID NO: 8, SEQ. ID NO: 9, SEQ. ID NO: 10, SEQ. ID NO: 11, SEQ. ID NO: 12, SEQ. ID NO: 13, SEQ. ID NO: 14, SEQ. ID NO: 15, SEQ. ID NO: 16, SEQ. ID NO: 17, SEQ. ID NO: 18, SEQ. ID NO: 19, SEQ ID NO: 20, SEQ. ID NO: 86, SEQ ID NO: 91, SEQ. ID NO: 92, SEQ. ID NO: 94, and mixtures thereof.

[0041] Non-limiting examples of sequences which are effective against the K6b keratin include but are not limited to SEQ. ID NO: 21, SEQ. ID NO: 22, SEQ. ID NO: 23, SEQ. ID NO: 24, SEQ. ID NO: 25, SEQ. ID NO: 26, SEQ. ID NO: 27, SEQ. ID NO: 28, SEQ. ID NO: 29, SEQ ID NO: 30, SEQ. ID NO: 31, SEQ. ID NO: 32, SEQ. ID NO: 33, SEQ. ID NO: 34, SEQ. ID NO: 35, SEQ. ID NO: 36, SEQ. ID NO: 37, SEQ. ID NO: 38, SEQ. ID NO: 39, SEQ. ID NO: 40, and mixtures thereof.

[0042] Similarly, non-limiting examples of sequences which are effective against the K16 keratin include but are not limited to SEQ. ID NO: 41, SEQ. ID NO: 42, SEQ. ID NO:43, SEQ. ID NO: 44, SEQ. ID NO: 45, SEQ. ID NO: 46, SEQ. ID NO: 47, SEQ. ID NO: 48, SEQ. ID NO: 49, SEQ. ID NO: 50, SEQ ID NO: 51, SEQ. ID NO: 52, SEQ. ID NO: 53, SEQ. ID NO: 54, SEQ. ID NO: 55, SEQ. ID NO: 56, SEQ. ID NO: 57, SEQ. ID NO: 58, SEQ. ID NO: 59, SEQ. ID NO: 60, and mixtures thereof.

[0043] Non-limiting examples of sequences which can be effective in inhibiting K17 keratin include but are not limited to SEQ. ID NO: 61, SEQ. ID NO: 62, SEQ. ID NO: 63, SEQ. ID NO: 64, SEQ. ID NO: 65, SEQ. ID NO: 66, SEQ. ID NO: 67, SEQ. ID NO: 68, SEQ. ID NO: 69, SEQ. ID NO: 70, SEQ. ID NO: 71, SEQ. ID NO: 72, SEQ. ID NO: 73, SEQ. ID NO: 74, SEQ. ID NO: 75, SEQ. ID NO: 76, SEQ. ID NO: 77, SEQ. ID NO: 78, SEQ. ID NO: 79, SEQ. ID NO: 80, and mixtures thereof.

[0044] The sequences set forth above are merely exemplary and are not intended to limit the present invention. Other sequences may also be used to inhibit the expression of any of the targeted keratin genes in order to treat the keratin hyperproliferation disorders taught herein. Such sequences could be readily identified and created by one of ordinary skill in the art using the methods and techniques set forth herein as well as others well known in the art.

Methodology

[0045] In order to show that hyperproliferative keratin-specific siRNA result in down-regulation of K6a expression, human 293FT cells were transfected with wildtype and mutant (as one control that should be unaffected by treatment—this particular single nucleotide mutation, used as control in these experiments, results in an asparagine to lysine amino acid change, N171K, and is one cause of the rare skin disorder pachyonychia congenita) forms of K6a fused to a reporter protein. In order to differentiate inhibition of wildtype versus mutant genes, a fluorescence-based FACS assay was used. The assay tests siRNA inhibitors against wildtype and mutant gene mRNA in which the target gene is fused to a reporter gene, in this case yellow fluorescent protein (YFP). Once the problematic target gene (e.g. in KP) is identified, siRNA inhibitors can be made that target various regions of the mRNA. Co-transfection experiments of wildtype and target mutation expression constructs reveal which inhibitors

potently inhibit the wildtype gene, with little or no effect on mutant expression. As a positive control, an eGFP-specific siRNA inhibitor can be co-transfected with the wildtype and mutant constructs. YFP and eGFP are nearly identical in sequence and there are no nucleotide differences in the target site for the eGFP siRNA inhibitor used. Identified inhibitors can be further tested to check whether endogenous pre-existing keratin expression can be inhibited and evaluate "off-target" effects. Next, the inhibitors can be evaluated in a mouse model in which the siRNA efficacy is tested on K6a targets fused to the reporter gene firefly luciferase (fLuc) and expression monitored by in vivo imaging.

EXAMPLES

Example 1

KP Lesions Express High Levels of K6, K16 and K17 Proteins

[0046] An immunostaining assay of three separate patient biopsies taken from patients were utilized to demonstrate that K6, K16, and K17 are overexpressed in KP lesions. Each tissue sample was formalin-fixed, paraffin-embedded, and immunostained with the Dako Envision System (catalog K4007, DakoCytomation, Denmark). The antibodies used were 1:10 dilution of K6 (Progen Biotecknik), a 1:10 dilution of K16 (Lab Vision), and a 1:10 dilution of K17 (Sigma). A 1:400 dilution of 488-conjugated goat anti-mouse secondary antibody was used for all stains. This is a sensitive system that utilizes horseradish peroxidase-conjugated secondary antibodies.

Example 2

Differential Inhibition of Mutant K6a/YFP vs. Wild-type by Mutant-Specific K6a SiRNAs in Tissue Culture Cells

[0047] A fluorescence-based tissue culture assay was developed and used to test siRNA inhibitors against wildtype and control (to demonstrate single nucleotide specificity) K6a mRNAs in which the target gene is fused to a reporter gene (YFP). SiRNAs designed to target the C513 region of the wildtype K6a gene were tested. A series of siRNA inhibitors (19+2 format) that target every possible sequence surrounding the C513 site were designed and synthesized (supplied by Dharmacon RNA Technologies). FIG. **2** shows the sequence walk of the siRNA inhibitors for the C513 site of K6a, as well as the amount of inhibition against the wildtype and control expression plasmids. Co-transfection experiments with K6a (WT)/YFP and K6a(control)/YFP expression constructs were performed. Each siRNA was co-transfected into 293FT tissue culture cells with a plasmid vector expressing either K6a(WT)/YFP mRNA or a similar construct expressing the K6a(control)/YFP mRNA. 48 hours following transfection, the cells were trypsinized and analyzed for YFP expression using a Becton Dickson FACScan using channel FL1 (530 nm emission filter). Five thousand cells per transfection were analyzed. The data were generated by gating the cells and determining the percentage of cells that dropped below the gate with and without siRNA treatment. As a positive control, eGFP-specific siRNA inhibitors were co-transfected with the wildtype and control K6a/YFP constructs (the 50% inhibitory concentration, IC_{50}, values were 0.1 nM against both constructs). No effect was observed with the irrelevant non-specific control (NSC4) siRNA inhibitor. The data were normalized and then corrected against cells transfected with the non-specific control. Specifically, the co-transfection experiments revealed several inhibitors including WT.4 and WT.12 (SEQ ID NOS: 86, 91, 92, and 94) that exhibit strong discrimination between wildtype K6a and mutant K6a targets (e.g. IC_{50} values for WT.12 were ~0.2 nM and >4 nM nM against the wildtype and mutant constructs, respectively as determined by FACS analysis). In order to further demonstrate the single nucleotide specificity of WT.4 and WT.12, additional siRNAs were synthesized containing all possible nts at position 513. FIG. **3** shows that only perfect complementarity (i.e. "c" in passenger siRNA strand, "g" in guide strand) results in inhibition of wildtype K6a expression.

[0048] These results show that siRNA inhibitors can have robust, specific and high inhibitory activity against wildtype K6a expression, with little or no effect on control K6a (differing by only one nucleotide) activity. As was expected, some of the designed inhibitors exhibited little or no inhibition against either wildtype or control expression.

Example 3

SiRNA-Mediated Down-Regulation of Pre-Existing K6a Expression in Human Keratinocytes

[0049] Human HaCaT keratinocytes were transfected with K6a-specific siRNAs (WT.4 and WT.12) to test their ability to inhibit endogenous K6a (FIG. **4**). 96 hr post-transfection, cells were lysed and subjected to electrophoresis on a 4-12% bis-tris gel, transferred to nitrocellulose and incubated with a K6-specific antibody (HaCaT cells express K6a but not K6b, unpublished data). A strong band was seen for K6 in untreated HaCaT cells and those treated with the transfection reagent RNAiMAX. In cells treated with either K6a-specific siRNA, WT.4 or WT.12, a dramatic reduction in the amount of K6a protein was observed upon increased concentration of siRNA. No or little effect was observed in cells treated with the control K6a-specific inhibitors, CON.4 or CON.12. The levels of Lamin A/C were unaffected upon addition on K6a-specific siRNA, showing the absence of generalized effects following siRNA treatment. These results indicate that the wildtype K6a siRNAs can inhibit endogenous K6 under conditions where control K6a siRNAs have little or no effect, further demonstrating single nucleotide specificity.

Example 4

Delivery and Effectiveness of SiRNA Inhibitors in Mouse Footpad Keratinocytes

[0050] Female FVB mouse footpads were intradermally injected with a WT or control version of a firefly luciferase reporter gene/K6a plasmid (pL2K6a(WT) or pL2K6a(control)), encoding a bicistronic mRNA comprised of the firefly luciferase and K6a open reading frames separated by the foot and mouth virus 2A element to allow equal expression of both fLuc and K6a. The noninvasive analyses of gene expression afforded by this approach allows for the repeated monitoring of reporter gene expression over multiple timepoints in the same group of animals, minimizing the number of mice needed while refining the data sets and maximizing the amount of information obtained. The mice were imaged for luciferase expression at multiple timepoints (typically ranging from 12-120 hours) post gene delivery. FIG. **5** shows the

image at the 24-hour timepoint (left paw was treated with control K6a siRNA and the right with WT.12 siRNA).

[0051] It is to be understood that the above-described methods, formulations, and experimentals are only illustrative of preferred embodiments of the present invention. Numerous modifications and alternative arrangements may be devised by those skilled in the art without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements.

[0052] Thus, while the present invention has been described above with particularity and detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention, it will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function and manner of operation, assembly and use may be made without departing from the principles and concepts set forth herein.

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<400> SEQUENCE: 57

ggagcagagc ucauccagcu u 21

<210> SEQ ID NO 58
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gcuggaugag cucugcuccu u 21

<210> SEQ ID NO 59
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<400> SEQUENCE: 59

cugagcugcc ucuaccacau u 21

<210> SEQ ID NO 60
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ugugguagag gcagcucagu u 21

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ggccaccaug cagaaccucu u 21

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gagguucugc augguggccu u 21

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cacugagcug gaggugaagu u 21

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cuucaccucc agcucagugu u 21

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gauccgugac ugguaccagu u 21

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cugguaccag ucacggaucu u 21

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<400> SEQUENCE: 67

uugaggagcu gcagaacaau u 21

<210> SEQ ID NO 68
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<400> SEQUENCE: 68

uuguucugca gcuccucaau u 21

<210> SEQ ID NO 69
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<213> ORGANISM: Artificial
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caagauccuc acagccaccu u 21

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gguggcugug aggaucuugu u 21

<210> SEQ ID NO 71
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gauccucaca gccaccgugu u 21

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cacgguggcu gugaggaucu u 21

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ugccaacauc cugcuacagu u 21

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cuguagcagg auguuggcau u 21

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<400> SEQUENCE: 75

cauccugcua cagauugacu u 21

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gucaaucugu agcaggaugu u 21

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gaagaaccac gaggaggagu u 21

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gaagaaccac gaggaggagu u 21

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gaagaaccac gaggaggagu u 21

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acagaucaag acccucaacu u 21

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cagaucaaga cccucaacau u 21

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aucaagaccc ucaacaacau u 21

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ucaagacccu caacaacaau u 21

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aagacccuca acaacaaguu u 21

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agacccucaa caacaaguuu u 21

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acccucaaca acaaguuugu u 21

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cccucaacaa caaguuugcu u 21

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ucaacaacaa guuugccucu u 21

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caacaaguuu gccuccuucu u 21

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gaucaagacc cucaaaaacu u 21

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gaucaagacc cucaagaacu u 21

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<210> SEQ ID NO 107
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<212> TYPE: RNA

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<400> SEQUENCE: 107

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cccucaauaa caaguuugcu u 21

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<223> OTHER INFORMATION: synthetic

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<210> SEQ ID NO 111
<211> LENGTH: 33
<212> TYPE: DNA
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1. A method of treating or preventing a hyperproliferation skin disorder in a subject,
comprising:
administering to the subject a therapeutically effective amount of an RNA sequence which inhibits expression of a gene encoding for a keratin selected from the group consisting of K6a, K6b, K16, K17, and combinations thereof.

2. The method of claim **1**, wherein the hyperproliferation skin disorder is selected from the group consisting of keratosis pilaris, calluses, corns, psoriasis, keratosis follicularis, pityriasis rubra pilaris, and Clouston syndrome.

3. The method of claim **2**, wherein the hyperproliferation skin disorder is keratosis pilaris.

4. The method of claim **2**, wherein the hyperproliferation skin disorder is a callus.

5. The method of claim **2**, wherein the hyperproliferation skin disorder is a corn.

6. The method of claim **1**, wherein the RNA sequence is a small interfering RNA.

7. The method of claim **1**, wherein the subject's overexpressed gene encodes keratin 6a (K6a).

8. The method of claim **1**, wherein the subject's overexpressed gene encodes keratin 6b (K6b).

9. The method of claim **1**, wherein the subject's overexpressed gene encodes keratin 16 (K16).

10. The method of claim **1**, wherein the subject's overexpressed gene encodes keratin 17 (K17).

11. The method of claim **6**, wherein the RNA sequence is a member selected from the group consisting of: SEQ. ID NO: 2, SEQ. ID NO: 4, SEQ. ID NO: 6, SEQ ID NO: 8 SEQ ID

NO: 10, SEQ ID NO: 12, SEQ. ID NO: 14, SEQ. ID NO: 16, SEQ. ID NO: 18, SEQ. ID NO: 20, SEQ. ID NO: 22, SEQ. ID NO: 24, SEQ. ID NO: 26, SEQ. ID NO: 28, SEQ. ID NO: 30, SEQ. ID NO: 32, SEQ. ID NO: 34, SEQ. ID NO: 36, SEQ. ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ. ID NO: 44, SEQ. ID NO: 46, SEQ. ID NO: 48, SEQ. ID NO: 50, SEQ. ID NO: 52, SEQ. ID NO: 54, SEQ. ID NO: 56, SEQ. ID NO: 58, SEQ. ID NO: 60, SEQ. ID NO: 62, SEQ. ID NO: 64, SEQ. ID NO: 66, SEQ. ID NO: 68, SEQ. ID NO: 70, SEQ. ID NO: 72, SEQ. ID NO: 74, SEQ. ID NO: 76, SEQ. ID NO: 78, SEQ. ID NO: 80, and mixtures thereof.

12. The method of claim **1**, wherein the siRNA sequence is administered as double stranded RNA.

13. The method of claim **1**, wherein the siRNA sequence is administered as a short hairpin RNA.

14. The method of claim **1**, wherein the RNA sequence has a length of about 15 to about 31 nucleotides.

15. The method of claim **1**, wherein the RNA sequence is administered transdermally.

16. The method of claim **15**, wherein the transdermal administration includes formulations and processes selected from the group consisting of: a lotion, a cream, a gel, an ointment, a paste, a transdermal patch, a liposome, iontophoresis, electroporation, sonophoresis, or combinations thereof.

17. The method of claim **1**, wherein the RNA sequence is administered by intradermal injection.

18. The method of claim **17**, wherein the intradermal injection is accomplished using dissolvable needles.

19. The method of claim **1**, wherein the RNA sequence is administered in a therapeutically effective amount of from about 0.1 mg to about 10 mg.

20. The method of claim **1**, wherein the RNA sequence contains at least one modified nucleotide.

21. The method of claim **1**, wherein the RNA sequence is administered in combination with a therapeutically effective amount of a compound selected from the group consisting of corticosteroid, lanolin, aloe vera, urea, propylene glycol, α-hydroxy acids, lactic acid, salicylic acid, vitamin D_3 and its derivatives, vitamin A and retinoids, levothyroxin, NSAIDS, cyclosporine, methotrexate sodium, anthralin, acitretin, tazarotene, coal tar, botulinum toxin, topical anesthetics, antihistamine, and combinations thereof.

22. The method of claim **1**, wherein the inhibited gene encodes for a mutated keratin.

23. The method of claim **1**, wherein the inhibited gene encodes a wildtype keratin.

24. The method of claim **20**, wherein the RNA sequence inhibits expression of both mutated and wildtype keratin genes.

25. The method of claim **1**, wherein the inhibited gene encodes the K6a keratin and the RNA sequence is a member selected from the group consisting of: SEQ. ID NO: 2, SEQ. ID NO: 4, SEQ. ID NO: 6, SEQ. ID NO: 8, SEQ. ID NO: 10, SEQ. ID NO: 12, SEQ. ID NO: 14, SEQ. ID NO: 16, SEQ. ID NO: 18, SEQ. ID NO: 20, SEQ. ID NO: 86, SEQ. ID NO: 91, SEQ. ID NO: 92, SEQ. ID NO: 94, and combinations thereof

26. The method of claim **1**, wherein the inhibited gene encodes the K6b keratin and the RNA sequence is a member selected from the group consisting of: SEQ. ID NO: 22, SEQ. ID NO: 24, SEQ. ID NO: 26, SEQ. ID NO: 28, SEQ. ID NO: 30, SEQ. ID NO: 32, SEQ. ID NO: 34, SEQ. ID NO: 36, SEQ. ID NO: 38, SEQ. ID NO: 40, and combinations thereof

27. The method of claim **1**, wherein the inhibited gene encodes the K16 keratin and the RNA sequence is a member selected from the group consisting of: SEQ. ID NO: 42, SEQ. ID NO: 44, SEQ. ID NO: 46, SEQ. ID NO: 48, SEQ. ID NO: 50, SEQ. ID NO: 52, SEQ. ID NO: 54, SEQ. ID NO: 56, SEQ. ID NO: 58, SEQ. ID NO: 60, and combinations thereof

28. The method of claim **1**, wherein the inhibited gene encodes the K17 keratin and the RNA sequence is a member selected from the group consisting of: SEQ ID NO: 62, SEQ. ID NO: 64, SEQ. ID NO: 66, SEQ. ID NO: 68, SEQ. ID NO: 70, SEQ. ID NO: 72, SEQ. ID NO: 74, SEQ. ID NO: 76, SEQ. ID NO: 78, SEQ. ID NO: 80, and combinations thereof

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