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(71) Applicant *(for all designated States except US)*: **NEXGENIX PHARMACEUTICALS, LLC.** [US/US]; 152 West 57th Street, Suite 11B, New York, New York 10019 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CHEN, Ruihong** [US/US]; 1031 Flying Fish, Foster City, California 94404 (US). **RUBENSTEIN, Allan E.** [US/US]; 15 West 81st. Street, Apt. 4G, New York, New York 10024 (US). **SHEN, Xiaodong** [CN/US]; 918 Beach Park Blvd., #54, Foster City, California 94404 (US).

(74) Agents: **HULEATT, Jayme** et al.; Cooley Godward Kronish LLP, 1200 19th Street, NW., Suite 500, Washington, District Of Columbia 20036 (US).

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(54) Title: LOCAL TREATMENT OF EPIDERMAL AND DERMAL HYPERPROLIFERATIVE LESIONS

(57) Abstract: A method for treating at least one epidermal or dermal hyperproliferative lesion in a subject in need of such treatment is disclosed. The method comprises locally applying a composition to a lesion either topically or intralesionally or via local delivery to the region in proximity to the lesion. Compositions useful for such treatments and methods of preparing the compositions are disclosed.

LOCAL TREATMENT OF EPIDERMAL AND DERMAL HYPERPROLIFERATIVE LESIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Application Serial No. 60/836,366, filed on August 9, 2006; the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Hyperproliferative lesions of the epidermis and dermis represent a significant health problem that in some instances may result in disfigurement. These lesions are generally caused by abnormal cell growth, differentiation, or apoptosis of keratinocytes, basal cells, skin fibroblasts, melanocytes, neural cells, or cells from other tissue origin. These abnormalities can be the results of viral infections, genetic alterations, or combination of both. These lesions or growths can be benign or malignant and may include the following conditions: viral warts, typically of the hands, plantar surface of the feet, and ano-genital area; basal cell carcinomas (BCCs), actinic keratoses (AKs), squamous cell carcinomas (SCCs), melanomas, pre-neoplastic lesions (e.g. nevi), cutaneous and subcutaneous hamartomas (e.g. neurofibromas), skin metastases of other tumors/cancers (e.g., cutaneous T cell lymphomas, skin lesions of Kaposi's sarcomas, etc.).

[0003] Viral cutaneous warts are benign epidermal proliferations induced by human papillomavirus (HPV) infection. Warts may exist in different forms according to the location and HPV type responsible for the infection. Common warts (Verruca vulgaris), plantar warts (Verruca plantaris), flat or planar warts (Verruca plana), and genital warts (Condyloma acuminata) are common forms. Warts are estimated to occur in 10 percent of children and young adults (between 12 and 16 years of age), and in 7-10% of the adult population. Viral warts can spontaneously clear after two years without treatment in 40 percent of children based on studies of the natural history of warts. Warts typically continue to increase in size and may become more resistant to treatment over time, particularly in adults.

[0004] An evidence-based review of therapeutic options for cutaneous warts published in 2005 (American Family Physician 72(4): 650, 2005) concluded that only acetylsalicylic acid and cryotherapy were unequivocally effective.

[0005] Basal cell carcinoma (BCC), first described by Jacob in 1827, is one of the most common malignancies in humans. The incidence rate has increased over the last 30 years (Mikkilineni R. and Weinstock M.A. Epidemiology of skin cancer. In: *Atlas of Clinical*

Oncology: Skin Cancer. London, UK: BC Decker, Inc., 2001: 1–15). Roughly one million new cases have been diagnosed annually in the United States since 1998 (Miller D.L. and Weinstock M.A. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol 1994; **30**:774–778.). Typically, BCCs occur in the fourth decade of life or later although exceptions to this occur, in particular in the setting of specific genodermatoses or in patients with immune compromise.

[0006] Arising from abnormal epidermal keratinocyte growth, a BCC is usually slow growing and rarely metastasizes. The three most common tumor subtypes are nodular (nBCC, 79%), superficial (sBCC, 15%), and morpheaform (6%) (Scrivener Y., Grosshans E., Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. *Br J Dermatol* 2002; 147: 41–47.) Lesions can occur on both sun-protected and sun-exposed skin. Even though BCCs are mostly benign, they still cause significant morbidity, such as disfigurement and local tissue destruction. Additionally, a condition known as the basal cell nevus syndrome (also called Gorlin's syndrome) predisposes patients to developing large numbers of BCC tumors, ranging from tens to thousands.

[0007] Squamous cell carcinoma (SCC) is a tumor of the keratinizing cells of the epidermis, typically appearing on the skin and mucous membranes. SCC occurs in more than 300,000 cases annually in the United States (American Cancer Society: Cancer Facts and Firures - 2002. Atlanta, GA, American Cancer Society, 2002). SCC of the skin is the second-most common skin malignancy. The factors that contribute to this epidemic are natural and artificial ultraviolet radiation exposure, white race, fair complexion, older age, male gender, occupational and recreational exposure to carcinogens, immunosuppression, and genetic susceptibility. Australia, for example, with its considerable sun exposure and a population high in light-skinned Caucasians, has the highest rate of skin SCC in the world.

[0008] The clinical appearance of SCC can be quite variable and may be influenced by the tumor's location and depth. Intraepithelial lesions such as actinic keratoses (AKs) are considered precursor lesions of SCC of the skin. They appear as crusted, hyperkeratotic, erythematous growths on the face, scalp, ears, arms, and hands. Squamous cell carcinoma is more likely to develop if these lesions are painful, ulcerative, or unresponsive to treatment. Squamous cell carcinoma in situ (also known as Bowen's disease) is a solitary lesion with superficial erythema and fine demarcated borders. Squamous cell carcinoma in situ can also appear as a whitish plaque on the mucous membranes of the oral cavity, a condition known as leukoplakia. Invasive SCC may develop from a preexisting actinic keratosis, SCC in situ, or

de novo from normal or damaged skin. These lesions are usually indurated, with poorly defined borders, and are more likely to be associated with symptoms such as bleeding or localized tenderness.

[0009] Current treatment options for BCC, AK, and SCC include surgical and non-surgical approaches with variable success rates. Surgical removal of tumors is the standard of care for BCC, AK, SCC *in situ*, and small, well-circumscribed SCC. Surgical treatments include surgical excision, curettage and electrodesiccation, Mohs micrographic surgery, and cryosurgery. Nonsurgical treatments include radiation therapy, photodynamic therapy, and pharmacologic treatments, such as topical 5-fluorouracil and topical imiquimod. There are disadvantages to the various treatment options. Surgical excision of sBCC and nBCC has a high 5-year recurrence rates if tumors are not completely excised. Multiple cycles of treatment are recommended for curettage and electrodesiccation and cryosurgery, which may lead to unsatisfactory results (e.g. scarring and hypopigmentation). Similarly, photodynamic therapy requires multiple cycles with variable cosmetic outcomes and recurrence rates. Mohs micrographic surgery is a useful treatment but is usually reserved for high-risk tumors, e.g. lesions that are recurrent or more than 2 cm in diameter or when perineural invasion is suspected. Fewer pharmacologic treatment options are available for consideration in the treatment of BCC. 5-FU may be effective for some superficial tumors long-term recurrence rates have not been established. Imiquimod, a novel immune response modifier, may be an efficacious and well-tolerated therapy of sBCC. However, localized skin reactions (e.g. erythema) and treatment duration (e.g. 6–12 weeks) may limit patient compliance, and long-term recurrence rates are not currently available. In addition, these treatments remain unsatisfactory for locally destructive, potentially metastatic basal-cell carcinomas.

[0010] Therefore, a need exists for a more satisfactory treatment of hyperproliferative lesions of the epidermis and dermis, that is efficacious and simple in its administration, such as local treatment of these lesions with therapeutic agents that will inhibit their growth or cause death of the tumor cells.

SUMMARY OF THE INVENTION

[0011] One aspect of the present invention is a method for treating at least one epidermal or dermal hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a cutaneous or a subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial

plexiform neurofibroma), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcomas, etc.) in a subject in need of such treatment.

[0012] In a further aspect of the present invention, the method comprises locally applying a pharmaceutical composition to the region or area in proximity to at least one epidermal or dermal hyperproliferative lesion, which includes administering the composition topically, intralesionally or by delivery or application to the region or area in proximity to the lesion so that the composition is delivered to the lesion.

[0013] In a further aspect of the present invention, the method comprises locally administering via topical application, intralesional application or by delivery or application to the region or area in proximity to the lesion, a composition to at least one epidermal or dermal hyperproliferative lesion, wherein the pharmaceutical composition comprises (a) at least one agent for abating the negative impact of the lesion on the subject, and optionally (b) a pharmaceutically acceptable excipient that aids in transporting the agent into the lesion where it is preferably maintained for a sufficient period of time to negatively impact the lesion.

[0014] Another aspect of the invention is a pharmaceutical composition that is useful for treating at least one epidermal or dermal hyperproliferative lesion via local administration, wherein the lesion may include a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcomas) and a cutaneous or subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject. The pharmaceutical composition comprises (a) at least one agent for abating the negative impact of the lesion on the subject, and optionally (b) a pharmaceutically acceptable excipient that aids in transporting the agent into the lesion, and preferably maintains the agent in the region or area in proximity to the lesion, on the subject's skin covering the lesion or in the lesion for a sufficient period of time for it to penetrate the lesion. The composition alternatively comprises (a) at least one agent for abating the negative impact of the lesion on the subject, and optionally, (b) a pharmaceutically acceptable carrier suitable for intralesional delivery or delivery into the region or area in proximity to the lesion so that the agent is delivered to the lesion. The excipient or carrier facilitates local delivery by either topical or intralesional administration of the agent to the lesion.

[0015] Still another aspect of the invention is a method of preparing a medicament for local administration which may include administration topically, intralesionally or by delivery into

the region or area in proximity to of at least one epidermal or dermal hyperproliferative lesion or growth with an agent that abates the negative impact of the hyperproliferative lesion or growth on a subject with a pharmaceutically acceptable topical excipient that aids in transferring the agent from the skin into the lesion and preferably maintains the agent on the skin and facilitates delivery of the agent into the lesion of the subject for a sufficient period of time for the agent to abate the negative impact of lesion. The delivery intralesionally or to the region or area surrounding or in proximity to the lesion may be facilitated by the excipient.

[0016] Other aspects of the invention may be apparent to one skilled in the art after reading the following detailed description.

DETAILED DESCRIPTION

[0017] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The use of the words "a" or "an" herein to describe any aspect of the present invention is to be interpreted as indicating one or more.

[0018] In carrying out the method of this invention, a pharmaceutical composition is applied locally to the surface of the skin in the region or area in proximity of at least one hyperproliferative lesion wherein the composition comprises an agent that abates the negative impact of the hyperproliferative lesion on a subject.

[0019] Within the meaning of the present invention, a epidermal or dermal hyperproliferative lesion is defined as including a viral wart, a basal cell carcinoma (BCC), an actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcomas) and a cutaneous or subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma). A viral wart within the meaning of the present invention includes but is not limited to a plantar wart (Verruca plantaris), a common wart (Verruca vulgaris), a mosaic wart, a planar or flat wart (Verruca plana), a periungual wart, a filiform wart, an oral wart and a genital wart (Condyloma acuminata).

[0020] Within the meaning of the present invention, local delivery of a pharmaceutical composition containing an active agent to treat or abate the negative impact of the lesion on the subject includes topical delivery to the skin above or around the lesion, intralesional

delivery directly into the lesion via delivery techniques described herein and also delivery to the tissue in the region or area in proximity to the lesion via delivery means described herein.

[0021] The pharmaceutical composition comprising at least one agent for treating the lesions may be applied in any of the known methods for locally applying a composition. Thus, the composition may be sprayed on, dabbed on, rubbed on, or adhered onto the skin using a patch or the like. In addition, it can be applied to the skin covering the lesion or directly into the lesion or into the tissue in the region or area in proximity to the lesion resulting in the transport of the agent into at least one epidermal or dermal hyperproliferative lesion using an injection, microinjection, electrophoretic, ultrasound, or radiofrequency mechanism. It can be delivered using a delivery system that is viral-based or pneumatic. The agent may be formulated as nanoparticles, dendrimers, or liposomes. The composition for intralesional delivery may take a form of a powder, liquid solution or suspension, a cream, a lotion, an ointment, a gel, or another composition which allows the composition to be maintained in the lesion or in close proximity to the lesion for a period of time that is sufficient to cause the agent to remain in or migrate into the lesion. The choice of excipients may be to facilitate the delivery and release of the agent or drug into the lesion. Such a pharmaceutically acceptable excipient may be a carrier that aids in maintaining or extending the duration of action of the agent on the lesion that is being treated. The excipient also may include known substances that could affect the release of the agent into the lesion, such as affecting the release of the agent over time to allow an immediate release followed by an extended or delayed release of the agent.

[0022] The pharmaceutical compositions of this invention may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, 5% dextrose in water or buffered sodium or ammonium acetate solution. Additionally, pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. The pharmaceutically acceptable excipient or carrier may also provide a mild analgesic or other compound or composition which functions to reduce any stinging or burning sensation that the subject may experience during delivery of the composition.

[0023] The composition is locally applied to the skin or via a technique that delivers the composition to the tissue in the region in proximity to at least one hyperproliferative lesion or intralesionally injected or otherwise delivered into the hyperproliferative lesion according to

the methods described herein or known to persons skilled in the art. By "proximity to at least one hyperproliferative lesion" is meant within at least 4 cm, at least 3 cm, at least 2 cm or at least 1 cm of the center of the lesion. Generally, the lesions are readily apparent and will cause disfigurations on the skin. Thus, the application of the composition will be directly to the surface of the skin that is in the region of the lesion. That region will be anywhere on the skin that will be transported across the skin and into the lesion to cause the active agent in the composition to act on the lesion. Once the composition is applied to the skin, it is maintained on the skin for a period of time which is sufficient to transport the agent across the skin into the lesion to abate the negative impact of a lesion on the subject.

[0024] For local delivery, that may include both topical and intralesional injection as well as local delivery to the region in proximity to the lesion, there are a variety of "active " drug delivery methods and passive drug delivery (a formulation with or without a penetration enhancer). All the technologies perturb the keratin layer of the epidermis to improve drug delivery, with energy of some type or mechanically. The methods include: iontophoresis; ultrasound, radiofrequency (RF) and micro-needles (dermabrasion). Needle-less injection technology, which is a microneedle attached to a CO_2 cartridge which forces drug through the skin can also be used. These technologies allow delivery of the drug or agent to the lesion or tumor by penetration or piercing of the keratin layer of the epidermis. This delivery is intended to encompass not only direct injection(s) into the lesion but also indirect injection(s) that deliver the drug or agent around, below or near the vicinity of the lesion, thus allowing the drug or agent to be delivered in close proximity to the lesion or tumor resulting in the entry of the drug into the lesion or tumor.

[0025] Abating the negative impact means that (1) the size of the lesion may stabilize and not increase, (2) the lesion may be reduced in size, or (3) the pain and/or itching associated with the lesion may be reduced. Preferably the size of the lesion is reduced significantly as the disfigurement caused by the hyperproliferative lesion is a major disadvantage of the condition. Also a physician's assessment of each lesion treated is useful to determine whether therapy results in abatement of the negative impact of the lesion(s). For example, the physician assesses if the lesion has cleared or disappears, the percentage reduction in the area and/or volume of the lesion, time to lesion clearance, and appearance of the lesion (necrotic vs. not necrotic) and the subject's self evaluation of pain and pruritus associated with each lesion treated.

[0026] Markers for determining whether a composition is acting to abate the negative impact on a subject include measuring the size of the lesion over a treatment period and interviewing

the subject to determine if there is a reduction in the level of pain in the subject. Other markers can be developed such as a proliferation index showing the rate of growth of the lesion, an apoptotic index showing the rate of death of the tumor cells, or vessel density. Other biomarkers which may be apparent to one skilled in the art can also be used to measure the success of the composition of this invention. For example, biomarkers that monitor the activation status of hedgehog pathway may be used to measure target inhibition in BCC tissues by the composition of this invention. In most cases, a baseline is established before treatment by measuring the size of the lesion, where possible, using a calipers or using a MRI imaging technique, or establishing an index for the untreated lesion. Once the baseline is established the treatment can begin and measurements can be taken periodically to determine the success of the treatment.

[0027] The agents that are useful as a single agent or as a combination of one or more agents in the composition for applying to the surface of the skin or intralesionally injected into the lesion or delivered locally to the region in proximity to the lesion are those that will abate the negative impact of the lesion on the subject. Preferred agents useful in the present invention are agents that are not carcinogenic. The FDA or IARC Monographs have lists of compounds/agents that are considered to be carcinogenic. For example, such agents may be a chemotherapeutic agent (e.g., an anti-neoplastic agent, a cytotoxin, or an anti-proliferative agent); a sclerosing agent; an antibiotic, an immunomodulator (e.g. an immunoregulator, an immunosuppressant, or an immunostimulant) or an anti-inflammatory agent, such as a nonsteroidal anti-inflammatory drugs (NSAID) or a Cox-1 & 2 inhibitor; an agent that modulates gene transcription, e.g. a HDAC (histone deactylase) inhibitor (e.g. FK228, trapoxin); an angiogenesis inhibitor; an agent that alters the structure, function, localization, or post-translational modification of small GTPases (e.g. farnesyl transferase inhibitors [R115777], isoprenyl cysteine transferase inhibitors (cysmethnil); an agent that acts as a chemopreventative agent such as vitamins, vitamin derivatives, antioxidants, nutritional supplements (e.g. fenretinide, green tea extract containing EGCG); an antifibrotic agent; an agent that targets apoptotic or an anti-apoptotic signaling; a kinase inhibitor (e.g. a protein kinase inhibitor or lipid kinase inhibitor); an alkylphospholipid; a protein chaperone inhibitor, such as a heat shock protein inhibitor (e.g., HSP90 inhibitor); an antifungal agent; an agent that restores the function of a mutated gene, such as an agent that suppresses non-sense mutations (e.g., gentamicin); a nucleic acid-based therapeutic agent; a phosphatase inhibitor; and a protease inhibitor or an agent that inhibts skin hyperplasia (e.g., actinic keraptos, melanoma, Kaposi's sarcoma, basal cell or squamous cell carcinomas or skin metastases of

other cancers). For topical treatment, the composition preferably contains a skin penetrant that aids in pushing the agent across the skin into the lesion.

[0028] Examples of chemotherapeutic agents that are useful are (1) an agent that interferes with DNA replication by topoisomerase inhibition, (2) an agent that disrupts the microtubule and/or mitotic spindle, (3) an agent that acts as alkylating or damaging agents to DNA, or (4) an agent that interferes with nucleotide synthesis, i.e., an antimetabolite. Specific chemotherapeutic agents include thiotepa. Each of these agents is well known by one of ordinary skill in the art and can be obtained from standard known sources.

[0029] Protein kinase inhibitors are compounds that target kinases that are hyperactivated in these hyperproliferative lesions, such as components of the Ras-activated mitogen activated protein kinase pathway (e.g. MEK and Raf kinases), receptor and non-receptor tyrosine kinases, and the AKT-mTOR pathway, which promote cell proliferation and survival, respectively. Lipid kinase inhibitors are compounds that target the phosphatidylinositol 3-kinase pathway, which is hyperactivated in these lesions and leads to enhanced cell survival.

[0030] Protein chaperone inhibitors are those that inhibit Heat Shock Protein function. Heat Shock Protein activity is required to maintain physiological protein levels of EGFR family of receptor tyrosine kinases (e.g. erbB2), Raf, a component of the Ras-Mitogen activated protein kinase pathway, in addition to numerous other signaling molecules.

[0031] Angiogenesis inhibitors are those that block (1) angiogenesis signaling cascade, such as Vascular Endothelial Growth Factor (VEGF) Receptor signaling, (2) extracellular matrix breakdown, such as that induced by the matrix metalloproteinases (e.g., halofuginone), (3) growth, survival, and migration of endothelial cells, or (4) unknown mechanism of action. Some of these compounds also fall under other categories. These angiogenic processes, among others, are needed to ensure adequate blood supply to a growing lesions and are attractive modes of therapeutic intervention for these epidermal and dermal lesions.

[0032] Cell-cell communication, both chemical and physical, between numerous cell types, including tumor cells (e.g. keratinocytes or melanocytes), endothelial cells, mast cells, and skin fibroblasts is likely to be essential for lesion progression and growth. Immunomodulators, such as calcineurin inhibitors that block transcription of cytokines and growth factors, are an efficient means to interfere with cell-cell signaling.

[0033] Agents which correct a specific mutation, such as gene replacement or gentamicin for repair of nonsense mutations, are also useful.

[0034] The present invention is more specifically described by the following preferred embodiments: The invention is directed to a method of treating at least one

hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma) and a cutaneous or subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject in need of such treatment, which method comprises locally administering a pharmaceutical composition to the region of at least one lesion, wherein the composition comprises (a) at least one agent for abating the negative impact of the lesion on the subject, and optionally (b) a pharmaceutically acceptable excipient that aids in transporting the agent into the lesion, where it is preferably maintained for a sufficient period of time to negatively impact the lesion within the meaning of the present invention.

[0035] The present method comprises local administration which includes topically applying the pharmaceutical composition to the surface of the skin in the region of the lesion. When the composition includes an excipient, this excipient aids in transporting the agent across the skin and into the lesion, and preferably maintains the agent on the skin of the subject to facilitate transport. Local administration also includes directly intralesionally delivering the composition into the lesion but is also intended to encompass indirectly injecting the composition to the region or area in proximity or close proximity to the lesion.

[0036] In another embodiment, the present method comprises local administration of a pharmaceutical composition comprising an agent, such as an antibiotic, a sclerosing agent and/or an antibiotic sclerosing agent. More specifically, the agent may be at least one agent comprising tetracycline or an analogue thereof, and more specifically, the agent comprises doxycycline or an analogue thereof. Still in a further embodiment, the present method is useful for treating at least one hyperproliferative lesion comprising at least one viral wart, such as a plantar wart (Verruca plantaris). But other warts, such as common warts (Verruca vulgaris), mosaic warts, planar or flat warts (Verruca plana), periungual warts, filiform warts, oral warts and genital warts (Condyloma acuminata) can be treated utilizing the present method.

[0037] The present method utilizes an agent comprising a chemotherapeutic agent, wherein (1) the agent interferes with DNA replication by topoisomerase inhibition; (2) the agent disrupts the microtubule and/or mitotic spindle in a cell of the lesion; (3) the agent acts as an alkylating or damaging agent to DNA in a cell of the lesion; (4) the agent interferes with

nucleotide synthesis or a combination thereof or a combination of two or more of these agents.

[0038] The agent delivered to the lesion by the present method comprises a sclerosing agent, an antibiotic, an immunomodulator, an immunoregulator, an immunosuppressant, an immunostimulant, or an non-steroidal anti-inflammatory agent; an agent that modulates gene transcription; an angiogenesis inhibitor; an agent that alters the structure, function, localization, or post-translational modification of small GTPases; a chemopreventative agent; an inhibitor selected from the group consisting of a protein kinase inhibitor, a lipid kinase inhibitor, a heat shock protein inhibitor, a protein chaperone inhibitor, a phosphatase inhibitor or a protease inhibitor; an anti-fibrotic agent; an alkylphospholipid; an agent that targets apoptotic or anti-apopotic signaling; a nucleic acid-based therapeutic agent; an agent that restores the function of a mutated gene; an alkylating agent, such as thiotepa or carboplatin; an anti-metabolite or a nucleoside analogue, such as triciribine, sangivamycin, or tubercidin; a topoisomerase inhibitor, such as podophyllotoxin;, a microtubule inhibitor, such as mebendazole; a sclerosing agent, an antibiotic, such as doxycycline or analogues thereof; an anti-inflammatory agent or a nonsteroidal anti-inflammatory agent (NSAID), such as celebrex or diclofenac; an agent that modulates gene transcription, such as a HDAC inhibitor comprising tricostatin A; a chemopreventative agent, such as a retinoid, such as fenretinide; an alkylphospholipid, such as miltefosine; a HSP90 inhibitor, such as geldanamycin derivatives, such as 17-AAG, radicicol or analogues thereof; halofuginone, gentamicin, rapamycin, or a combination thereof.

[0039] The pharmaceutical composition containing any one or more of the above-identified agents may include as an excipient an analgesic to reduce stinging and/or burning for local administration including topical and intralesional. The excipient also may include a skin penetrant for topical administration.

[0040] Within the meaning of the present invention, the agent in the pharmaceutical composition does not include or is not an aliphatic alcohol. The agent for treating the lesions within the context of the present invention, particularly is not a C18 to C26 aliphatic alcohol as defined in U.S. 5,948,822, such as n-docosanol.

[0041] Also disclosed in the present invention are preferred pharmaceutical compositions useful for treatment of at least one hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma)

and a cutaneous or subcutaneous hamartomas, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject in need of such treatment.

[0042] The composition useful in the present method for locally treating at least one hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma and a cutaneous or subcutaneous hamartomas, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject in need of such treatment, which composition comprises (a) at least one agent for abating the negative impact of the lesion on the subject, and optionally (b) a pharmaceutically acceptable excipient for local delivery to include topical, intralesional or general delivery to the tissue surrounding the lesion that aids in transporting the agent into the lesion, and preferably maintains the agent on the subject's skin for a period of time.

[0043] The composition useful for delivery in the present invention comprises an agent that is a chemotherapeutic agent, wherein (1) the agent interferes with DNA replication by topoisomerase inhibition; (2) the agent disrupts the microtubule and/or mitotic spindle; (3) the agent acts as an alkylating or damaging agent to DNA; (4) the agent interferes with nucleotide synthesis or a combination thereof.

[0044] The agent delivered to the lesion by the present method comprises a sclerosing agent, an antibiotic, an immunomodulator, an immunoregulator, an immunosuppressant, an immunostimulant, or an non-steroidal anti-inflammatory agent; an agent that modulates gene transcription; an angiogenesis inhibitor; an agent that alters the structure, function, localization, or post-translational modification of small GTPases; a chemopreventative agent; an inhibitor selected from the group consisting of a protein kinase inhibitor, a lipid kinase inhibitor, a heat shock protein inhibitor, a protein chaperone inhibitor, a phosphatase inhibitor or a protease inhibitor; an anti-fibrotic agent; an alkylphospholipid; an agent that targets apoptotic or anti-apopotic signaling; a nucleic acid-based therapeutic agent; an agent that restores the function of a mutated gene; an alkylating agent, such as thiotepa or carboplatin; an anti-metabolite or a nucleoside analogue, such as triciribine, sangivamycin, or tubercidin; a topoisomerase inhibitor, such as podophyllotoxin; a microtubule inhibitor, such as mebendazole; a sclerosing agent, an antibiotic, such as doxycycline or analogues thereof; an anti-inflammatory agent or a nonsteroidal anti-inflammatory agent (NSAID), such as

celebrex or diclofenac; an agent that modulates gene transcription, such as a HDAC inhibitor comprising tricostatin A; a chemopreventative agent, such as a retinoid, such as fenretinide; an alkylphospholipid, such as miltefosine; a HSP90 inhibitor, such as geldanamycin derivatives, such as 17-AAG, radicicol or analogues thereof; halofuginone, gentamicin, rapamycin, or a combination thereof. The pharmaceutical composition containing any one or more of the above-identified agents may include as an excipient an analgesic to reduce stinging and/or burning and for topical administration, the excipient may include a skin penetrant. Also as noted above, the agent does not include or is not an aliphatic alcohol. The agent particularly is not a C18 to C26 aliphatic alcohol as defined in U.S. 5,948,822, such as n-docosanol.

[0045] The present invention also encompasses the use of the composition containing any of the agents or drugs described herein for the preparation of a pharmaceutical composition for the treatment of at least one hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma) and a cutaneous or subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject.

[0046] Additionally, the present invention discloses a method of preparing a medicament or pharmaceutical composition comprising the composition containing any one of agents or drugs as described herein for locally treating at least one hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma) and a cutaneous or subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma), which method comprises combining at least one agent for abating the negative impact of the lesion on the subject with a pharmaceutically acceptable for local delivery to include an excipient for topical, intralesional or general delivery to the tissue surrounding the lesion that aids in transporting the agent(s) into the lesion and preferably maintains the agent(s) on the skin of the subject for a period of time.

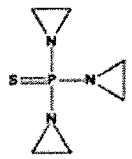
[0047] Examples of specific compounds alone or in combination that are useful in this invention as an agent for abating the negative impact of an epidermal or dermal

hyperproliferative lesion on a subject include thiotepa, doxycycline, sangivamycin, carboplatin, mebendazole, halfuginone, gentamycin, rapamycin, miltefosine, and the like.

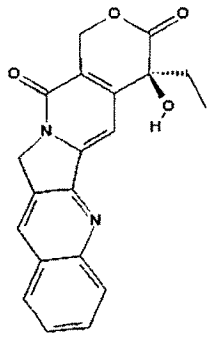
[0048] Further, the agent(s) contained in the compositions either as the single pharmaceutically active agent or in combination with one or more pharmaceutically active agents with or without a pharmaceutically acceptable topical excipient or other types of pharmaceutically acceptable excipients for abating the negative impact of the epidermal or dermal hyperproliferative lesion on a subject, includes but are not limited to the following agents:

1. Chemotherapeutic agents, such as cytotoxins, anti-neoplastic or anti-proliferative agents, for example: agents such as:

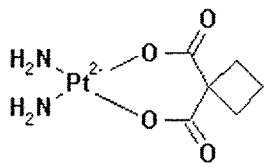
An alkylating agent, such as Thiotepa,



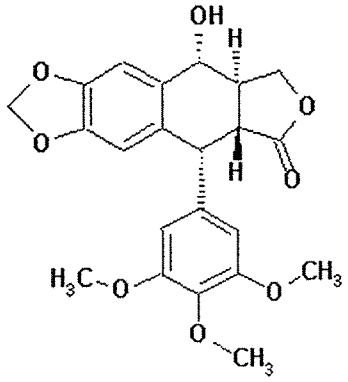
A topoisomerase inhibitor, such as Camptothecin,



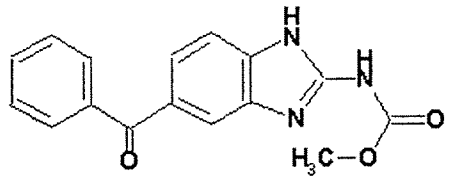
Carboplatin,



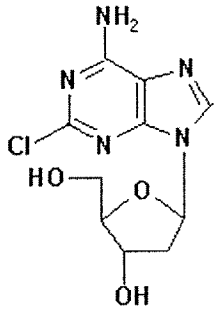
A topoisomerase inhibitor, such as Podophyllotoxin,



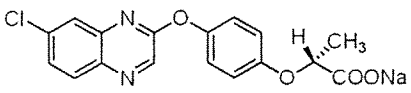
A microtubule inhibitor, such as Mebendazole,



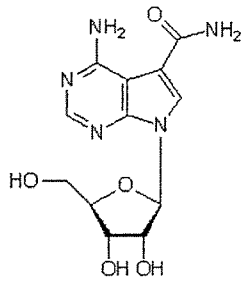
An antimetabolite or a nucleoside analogue, such as Cladribine



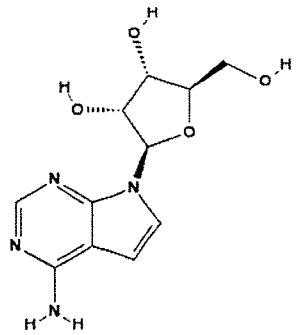
A topoisomerase inhibitor, such as XK469 (2-(4-((7-Chloro-2-quinoxalinyl)oxy)-phenoxy)propionic acid),



A nucleoside analogue, such as Sangivamycin

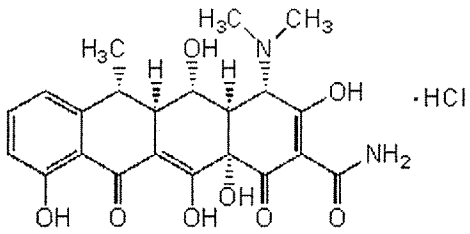


A nucleoside analogue, such as Tubercidin,



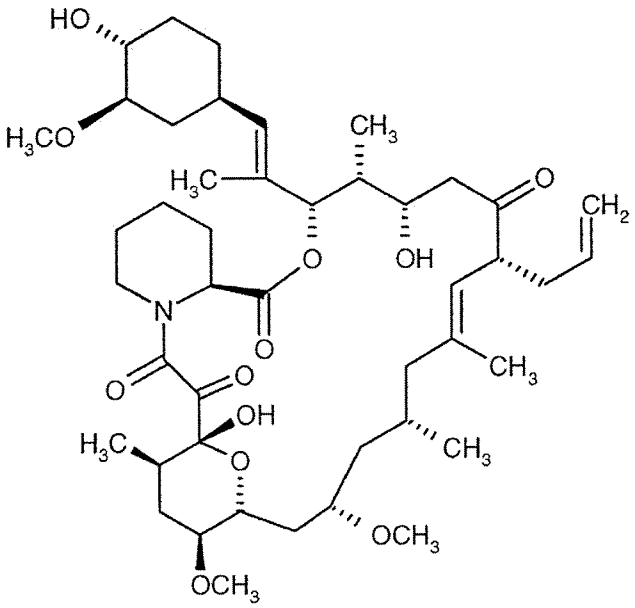
2. Antibiotics, for example:

   A tetracycline analogue or antibiotic, such as Doxycycline



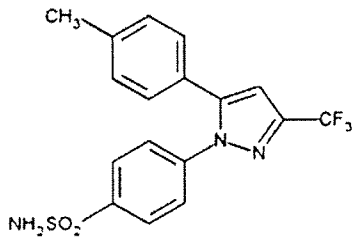
3. Immunomodulators or immunoregulators or immunostimulants or immunosuppressants, for example:

   Immunosuppressants, such as Tacrolimus (FK506)



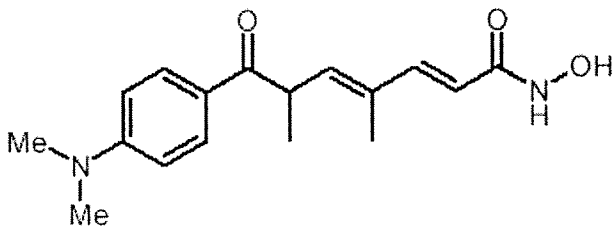
4. An anti-inflammatory agent or non-steroidal anti-inflammatory drug (NSAID), such as:

Celecoxib (also a Cox-1 & 2 inhibitor or an anti-inflammatory agent),

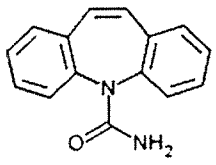


5. Agents that modulate gene transcription; e.g. HDAC (histone deactylase) inhibitors, for example:

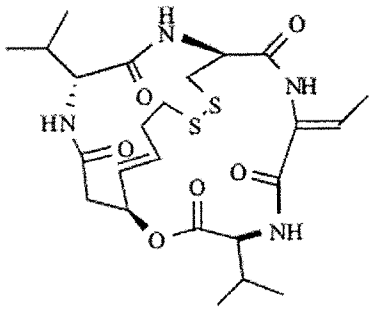
A hydroxamic acid class of HDAC inhibitors, such as Tricostatin A (TSA)



Carbamazepine (below) and its derivatives such as carbamazepine epoxide,

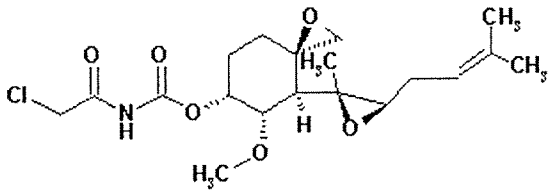


A cyclic tetrapeptide class of HDAC inhibitors, such as depsipeptide FK228 (FR901228),

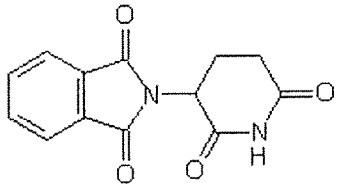


6. Angiogenesis inhibitors, for example:

A fumagillin, which is secreted by the fungus *Aspergillus fumigatus*, and its analogues such as TNP-470 [O-(Chloroacetylcarbamoyl) fumagillol] shown below:

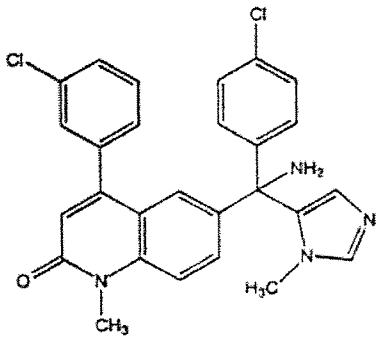


Thalidomide, also an immunomodulatory agent

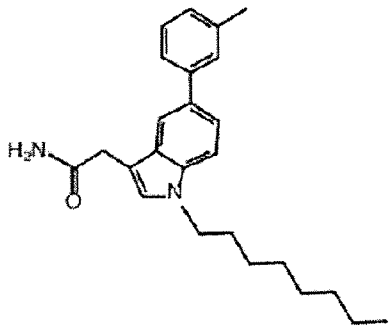


7. Agents that inhibit the cellular process that required for the modification of small GTPases such as:

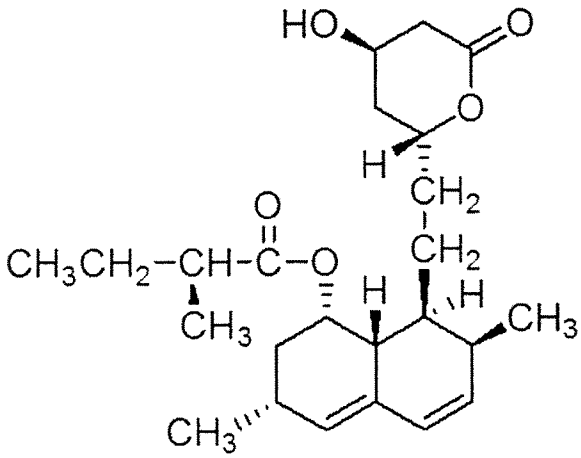
Farnesyl transferase inhibitors [e.g. R115777, (B)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone],



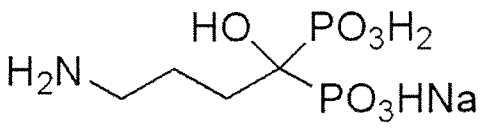
Isoprenyl cysteine transferase inhibitors [e.g. cysmethnil]



HMG-CoA inhibitors (statins, e.g. lovastatin)

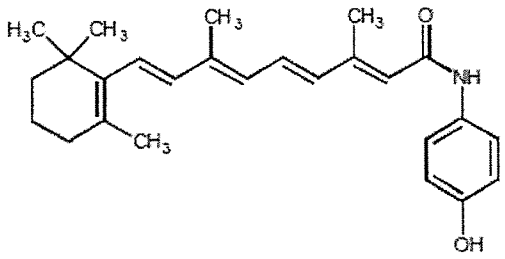


Bisphosphonates (e.g. alendronate, as inhibitors of mevalonate pathway)

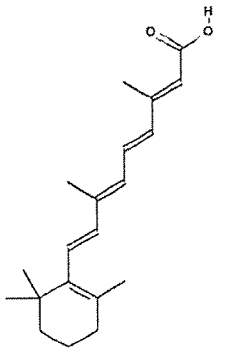


8. Chemopreventative agents, for example:

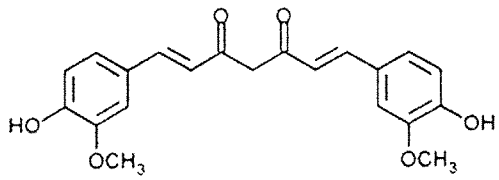
Synthetic retinoids (e.g. Fenretinide)



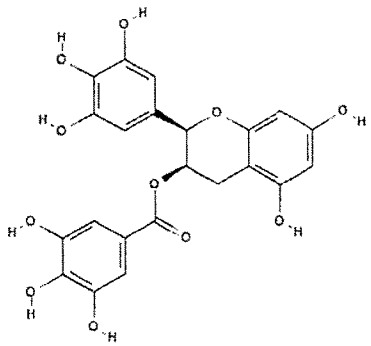
Retinoic acid [3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-nona-2,4,6,8-tetraenoic acid] and analogs,



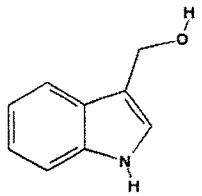
Curcumin and derivatives,



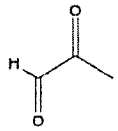
EGCG, (-)-Epigallocatechin Gallate (see below) and analogues



I3C (Indole-3-carbinol),

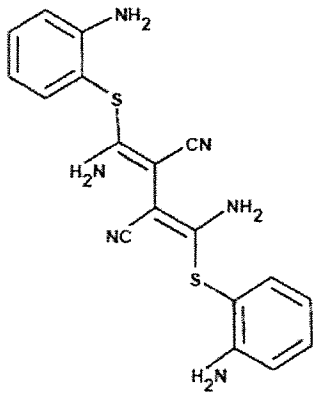


Methylglyoxal,

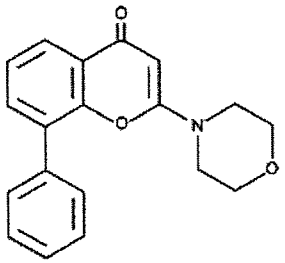


9. Kinase inhibitors, MEK inhibitors, Raf inhibitors, mTOR inhibitors, PI3K pathway inhibitors (e.g. PI3K inhibitors and AKT inhibitors),
examples, such as:

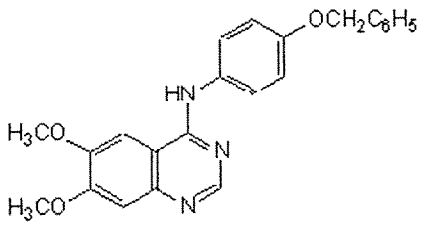
MEK inhibitors, such as U0126 [1,4-Diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)-butadiene],



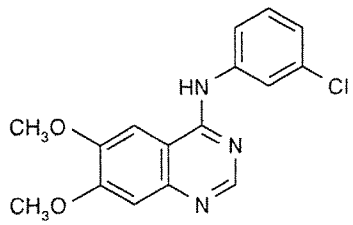
P13K inhibitors, such as Ly294002 [2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one]



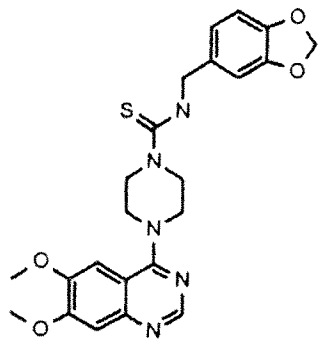
EGFR/ErbB2 inhibitors, such as 4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline,



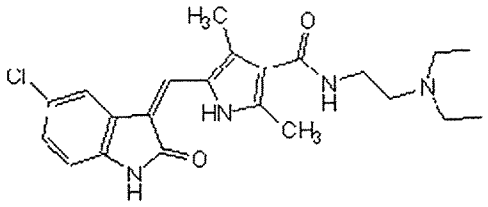
AG1478 (EGFR inhibitor), 4-(3-Chloroanillino)-6,7-dimethoxyquinazoline



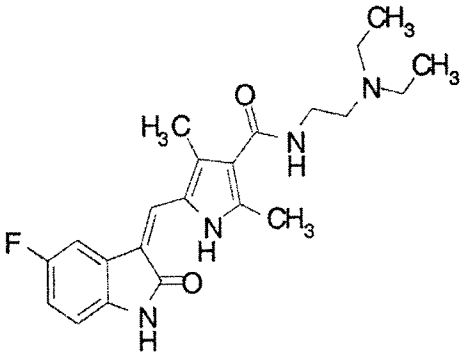
Inhibitors of multiple tyrosine kinases, e.g. PDGFR inhibitors such as KN2941 (4-(6.7-dimethoxy-4-quinazolinyl)-N-(3,4-methylenedioxybenzyl)-1-piperazinethiocarboxamide)



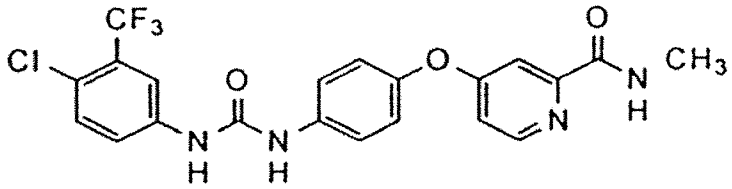
Inhibitors of multiple kinases such as SU11652, 5-[(Z)-(5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-N-[2-(diethylamino)ethyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide



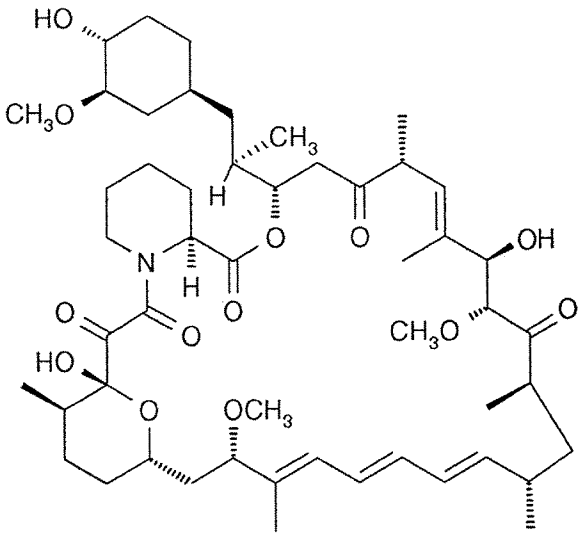
Inhibitors of multiple kinases such as SU11248 (Trade name is Sutent), 5-[(Z)-(5-Fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-N-[2-(diethylamino)ethyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide



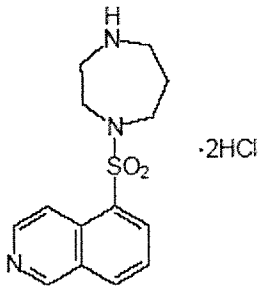
Inhibitors of multiple kinases e.g.VEGFR2 and Raf kinases such as Bay43-9006 (NEXAVAR, or Sorafenib), 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N2-methylpyridine-2-carboxamide



mTOR inhibitors, such as Rapamycin (also an immunosuppressant, see below) and prodrugs or analogues,

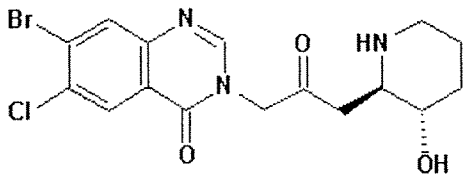


Rho kinase inhibitors such as Fasudil, [1-(5-Isoquinolinesulfonyl)homopiperazine]

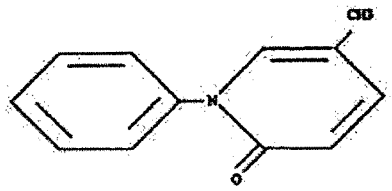


10. Novel antifibrotics, which may include agents that are also angiogenesis inhibitors, for example:

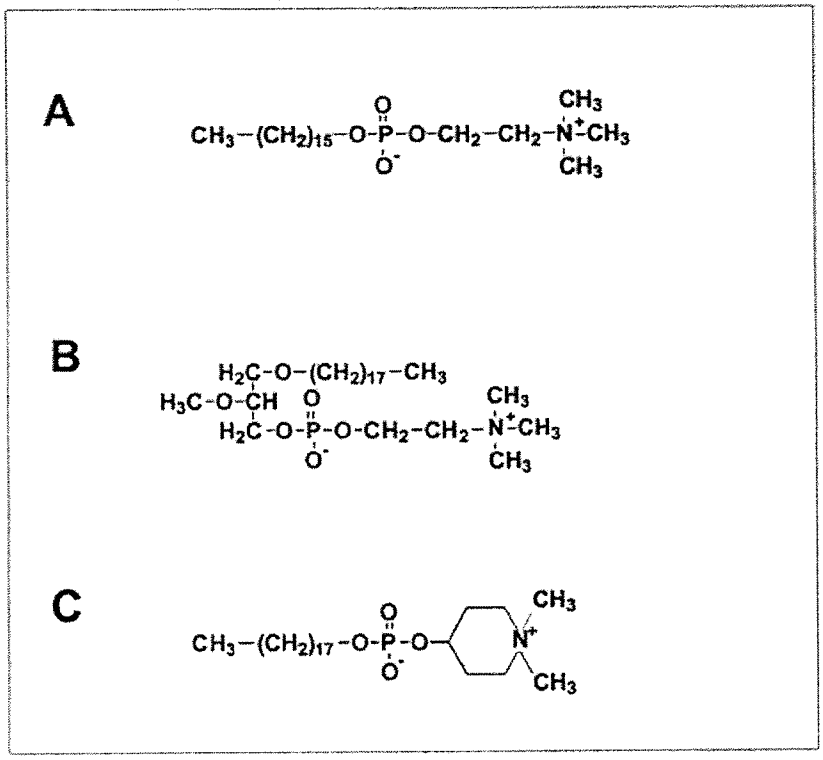
Halofuginone hydrobromide [(+/-)-trans-7-Bromo-6-chloro-3-[3-(3-hydroxy-2-piperidinyl)-2-oxopropyl]-4(3H)-quinazolinone hydrobromide]



Pirfenidone (5-Methyl-N-phenyl-2-1H-pyridone-d5)

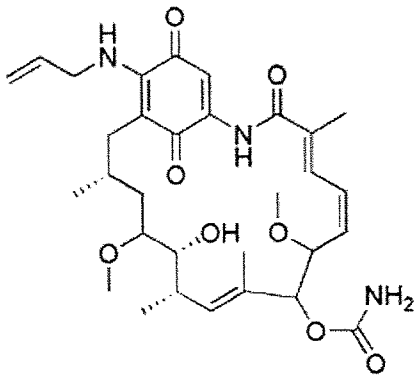


11. Alkylphospholipids, for example:
    A. Miltefosine (HePC)
    B. Edelfosine (Et-18-OCH3)
    C. Perifosine (D21266)

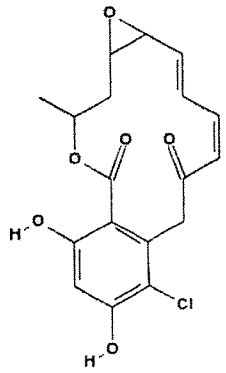


12. HSP90 inhibitors (heat shock protein inhibitors)

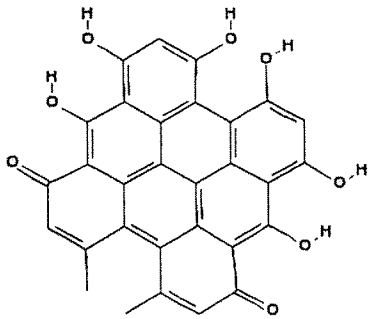
    Geldanamycin analogues/derivatives such as 17-AAG and its derivatives, 17-AAG, 17-(Allylamino)-17-demethoxygeldanamycin,



Radicicol and analogues,

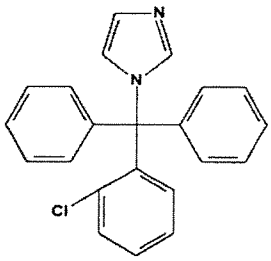


Hypericin



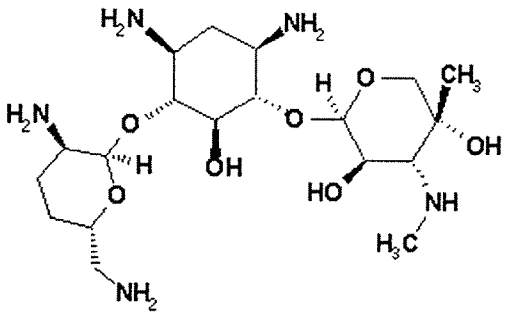
13. Antifungal agents:

Clotrimazole and analogs,



14. Agents that restore the function of a mutated gene, e.g. agents that suppress non-sense mutations, for example:

Gentamicin



[0049] In preparing compositions of this invention one is guided by the teachings of (1) Remingtons Pharmaceutical Sciences, Mack Publishing Co., 17th, 18th, or 19th Edition, ISBN:0-912734-04.3, (Also called "Remington: The Science and Practice of Pharmacy"); (2) Pharmaceutics – The Science of Dosage Form Design, Aulton, Churchill Livingston; (3) Appleton and Lange Review of Pharmacy (7th or 8th Ed) by Hall and Reiss, Appleton and Lange; and the like, all of which are incorporated herein by reference. For nanoparticle or liposome delivery, more information is available at http://www.happl.com/special/mar013.htm and http://www.collabo.com/liposome.htm. Information relating to dendrimer technology is found at http://www.ringer.com/dedrimer/one.htm.

[0050] The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable excipient, vehicle, diluent or carrier. Thus, the agents or drugs of the present invention can be administered individually or together in any conventional local, parenteral, intralesional or transdermal dosage form.

[0051] For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intralesional, intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well known to those skilled in the art.

[0052] For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 20% concentration), otherwise similar to the above parenteral solutions, are prepared.

[0053] Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 19th Edition (1995). All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986), herein incorporated by reference in its entirety.

Examples

[0054] Agents useful to treat epidermal or dermal hyperproliferative lesions in the present invention may be selected by several methods described herein. For example, various compounds/agents described herein as well as other agents that may be selected are tested in cell-based assay for their potency to inhibit cell proliferation of a panel of cell lines derived from such lesions and are tested to determine an effect on animal models of such lesions.

I. In Vitro Assays

1) Cell proliferation assays

[0055] Several physiologically relevant cells or cell lines are employed to measure compound potency in cell proliferation assays. These cells include: Basal cell carcinoma (BCC) cells (e.g. TE354.T, ATCC CRL-7762), paired benign BCC and normal (e.g. ATCC CRL-7805 and CRL-7804), human keloids fibroblasts (e.g. ATCC CRL-1762) and normal skin fibroblasts (e.g. ATCC CRL-1900), and mouse BCC cells derived from BCC tumors that arose in irradiated Patched 1 (*Ptch1+/-*) mice as described in So, P. et al., Long-term establishment, characterization and manipulation of cell lines from mouse basal cell carcinoma tumors. *Experimental Dermatology* 2006, **15**:742-750.

[0056] To perform cell proliferation assays, appropriate numbers of cells that can reach ~70% confluence in 3 days (for example, 2000 – 8000 cells/well depending on the cell line) are plated in 96-well plates in growth media commercially available and known to persons skilled in the field. Various concentrations of each compound/agent to be tested or vehicle alone are added to the growth media and the cells were then cultured for 3 days. Presumably, cells treated with the vehicle should reach ~70% confluency. Upon completion of the incubation, media are gently removed and 100 µl of ATPlite solution (Perkin Elmer, Boston, Cat.# 6016941) is added to each well. Viable cells are measured by detecting luminescence generated from reaction of ATPlite solution and the ATP in the cells. Potency ranges of various compounds/agents to inhibit cell proliferation of several such cell lines are determined. The selection criteria for agents/compounds that are useful as good candidates for the local treatment of hyperproliferative lesions is based on the selection of any compounds with an IC50s equal or below 10 µM (IC50 is defined as the concentration of an inhibitor that is required for inhibition of cell proliferation by 50% as compared to the vehicle control). Preferably, compounds with selective inhibition of tumor cells will have higher priority to test in the following assays. Selective inhibition is a ratio defined by the IC50 to inhibit normal cells divided by the IC50 to inhibit tumor cells. The ratio is preferred to be greater than 2. In addition, if compounds are believed to have mechanisms of actions that are non-cell autonomous (e.g. immunomodulatory or anti-angiogenesis) or unknown, they may not score as positives but they will be tested in animal models and in the proof-of-principle clinical trials in human subjects with hyperproliferative lesions if possible.

2) Animal assay

[0057] The efficacy of the compound is tested in a tumor burden reduction study in mouse models of BCC as described in Athar, M. et al., Inhibition of *smoothened* signaling prevents ultraviolet B-induced basal cell carcinomas through regulation of Fas expression and apoptosis. *Cancer Res.* 2004, **64**: 7545-7552 and in Adolphe C. et al., Patched1 functions as a gatekeeper by promoting cell cycle progression. *Cancer Res.* 2006, **66**:2081-2088. Briefly, *Ptch1*+/- heterozygous knockout mice (see Goodrich L. V. et al., Altered neural cell fates and medulloblastoma in mouse patched mutants. *Science* 1997, **277**:1109–1113) are UV-irradiated (240 mJ/cm2 three times a week) from age 6 to 32 weeks until ~50% of the animals have one or more visible skin tumors. The mice (25 mice per group) are given either different doses of drugs or the vehicle control (as the negative control) intralesionally in the volume of 50 µl. The doses of the drugs or agents are determined and selected based upon the data obtained in the *in vitro* studies discussed above or using standard techniques known

to persons skilled in the art. One tumor per mouse is injected and followed. Mice are weighed twice weekly, and tumor measurements are obtained using calipers twice weekly, starting on Day 1 of treatment. Tumor volumes were calculated by the standard formula $(W^2 \times L)/2$, where L is the length and W is the width. (Blaskovich MA, Lin Q, Delarue FL, Sun J, Park HS, Coppola D, Hamilton AD, Sebti SM (2000), Design of GFB-111, a platelet-derived growth factor binding molecule with antiangiogenic and anticancer activity against human tumors in mice. *Nat Biotechnol* **18**: 1065–1070). Depending on the compounds/drugs tested, the treatment can last for 4-20 weeks. At the end of study, tumors are harvested and processed for histologic and immunohistochemical studies. The effect of the compound is determined by either of: 1) tumor volume measurements – the tumor volume differences before and after treatment in both treated and control groups are analyzed using Student's t test. The result of a certain dose of the compound is considered to be "+" when the difference in tumor volume is statistically significant ($p<0.05$). 2) histological analysis - three histological parameters are used to score the samples. A) tissue necrosis - the picture of each sample at 40X under a bright field microscopy is taken using MagnaFire digital camera (Optronics, USA) and stored in computer. The necrosis areas in the pictures are measured using Photoshop and calculated as Length x Width, and then expressed as a percentage over the total area of the sample. Overall tissue necrosis is scored using 0 to 2+ score. In short, absence of necrosis is scored 0 (<5%), 1+ indicates medium tissue necrosis (5-25%), 2+ high tissue necrosis (>25%). Only 2+ cases are regarded as positive "+" for the final total score. B) tissue cellularity - the low cellularity area in the treated samples is defined as >30% less nucleus than the similar area on the control sample. The picture of each sample at 40X under a bright field microscopy is taken using MagnaFire digital camera (Optronics, USA) and stored in computer. The low cellularity areas in the pictures are measured using Photoshop and calculated as Length x Width, and then expressed as a percentage over the total area of the sample. Overall tissue integrity is scored using 0 to 2+ score. In short, good tissue integrity is scored 0 (<5%), 1+ indicates medium tissue integrity (5-25%), 2+ low tissue integrity (>25%). All 1+ and 2+ cases are regarded as positive "+" for the final total score. C) inflammatory cells infiltration - slides are evaluated by bright field microscopy. At least 100 cells per view are counted and the number of inflammatory cells per 100 total cells is calculated as a percentage for each sample. Inflammatory cells infiltration is determined by the difference between the percentage of the treated samples with that of the control sample and scored semi-quanlitatively using the 0 to 3+ score. In short, absence of or very low difference in inflammatory cells infiltration is scored 0 (<5%), 1+ indicates medium level of

Inflammatory cells infiltration (5-25%), and 2+ high level of inflammatory cells infiltration (>25%). All 1+ and 2+ cases are regarded as positive "+" for the final total score. Final histological score is the sum of the scores of the above three parameters, expressed as "-" to "+++". Any compound with either one "+" or more "+" in tumor volume measurement or a histological score of one "+" or more "+" will be potential good candidates for local treatment of hyperproliferative lesions.

[0058] The compounds/agents above can be tested using one or more of the above assays to select agents useful in the present invention to treat hyperproliferative lesions. The assays are preferably run in a particular order and when "positive results" are obtained, then the next assay is performed and so on. For example if an agent is tested in the cell proliferation assay and is positive by the criteria disclosed above, then this agent is tested in the animal assay. If both assay results are positive based on the criteria for a specific agent or compound, then this agent is expected to be a good candidate for successful treatment of hyperproliferative lesions. In addition, for compounds that are believed to have mechanisms of actions that are non-cell autonomous (e.g. immunomodulatory or anti-angiogenesis) or unknown, they are expected to be good candidates for successful treatment of hyperproliferative lesions if positive results are obtained in animal models, or in the proof-of-principle clinical trials with patients having hyperproliferative lesions if possible.

II. In Vivo Studies

General Study Design for Local Treatment of Nodular BCC Lesions with an Agent or Compound

A. Intralesional Administration

[0059] The study is a proof-of-concept, prospective, safety and efficacy study of the effect of intralesionally administered drugs given once a week or twice a week to 1 target nodular BCC lesion for 4 consecutive weeks. Fifteen to twenty subjects will be enrolled. All subjects should have the diagnosis of nodular BCC lesions possessing at least 2 such lesions 0.5 to 1.5 cm, inclusive. All subjects are from 18 to 65 years of age, inclusive. All subjects otherwise are in good health, or have stable concomitant medical conditions appropriately managed by a primary care physician. Enrolled subjects demonstrate no clinically significant abnormalities on both laboratory and physical examination, other than the features of BCC. After screening and enrollment, all subjects receive a defined volume (based on the size of the lesion) of intralesional drug once or twice weekly into the target nodular BCC lesion that are 0.5 to 1.5 cm in diameter, inclusive. Concomitantly, one control lesion of the same range

in sizes on the same subject receives sterile normal saline. All lesions prior to injection are locally anesthetized with lidocaine 1% and epinephrine 1:100,000. During the study period, subjects receive 4 week of intralesional injections at the 2 lesions (1 target lesion receiving drug, 1 control lesion receiving normal saline), and are followed every week during receipt of the study medication and three weeks after the last dose has been administered. At every visit, subjects undergo physical examinations, recording of adverse events and concomitant medications, and measurement and photography of both the target and control lesions. Assessment includes the exact measured dimensions (in two axes) of the two assessed lesions. Photography entails standardized digital images of both the target and control lesions (accompanied by a ruler) without any identifying features of the subject represented. For each subject, photography involves consistent focal length, lighting, and angle of exposure carried over from visit to visit. On each visit, each subject is questioned for potential side effects of the receipt of the study medication either during its administration or in between visits, including pain, pruritus, irritation, discoloration, ulceration, or any other new sign or symptom – either local or distant from the target and control lesions – not present at baseline.

[0060] To further evaluate the efficacy of doxycycline, subjects with plantar warts are selected for intralesional treatment with a pharmaceutical composition containing doxycycline. The lesion size must be within the range of 3 to 15 mm in diameter that has been present for 6 months or longer and the lesions should be easily accessible for treatment, photography, and evaluations. To establish a baseline, each target lesion is mapped to anatomical structures, is assigned a code for data identification, assessed clinically and baseline photographs are obtained. Subjects also complete baseline subjective and lesion assessment questionnaires.

[0061] Each target lesion will receive 25, 75 or 150 mg/mL doxycycline injection or placebo (containing 0.9% sodium chloride – normal saline) according to a random code.

[0062] The primary endpoint is the % of treated warts (across subjects for a given dose) cleared by the end of the study. This evaluation is based on the assessment of lesion presence or absence by a physician who assesses each lesion to determine if the lesion remains has cleared, partially cleared or remains. The physician utilizes an Inventigator Global Evaluation (IGE) scale for cutaneous warts. The physician is evaluating % reduction in wart area and/or volume. Other measures in the trial include: lesion size and calculated volume, time from treatment to lesion clearance, lesion appearance (necrotic vs. not necrotic), and a physician assessment of each lesion. In addition, subjects will evaluate pain, pruritus for each lesion.

B. Topical Administration

[0063] The subjects with hyperproliferative lesions are selected as described above in A, and similar controls are run with untreated lesions on the same subject. Alternative methods of administration include topical application by applying a composition containing any one or more of the agents described herein, in combination with 5% gel in sufficient quantities to the skin covering a lesion to cover the tumor once a day for 21 days. Additionally, topical application is performed by applying a dermabrasion device in which the device's micro-needles are coated with the composition comprising the agent to the skin covering the tumor once a day for 7 days.

We Claim:

1. A method of treating at least one hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma) and a cutaneous or subcutaneous hamartoma, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject in need of such treatment, which method comprises locally administering a pharmaceutical composition to the region of at least one lesion, wherein the composition comprises (a) at least one agent for abating the negative impact of the lesion on the subject, wherein the agent is non-carcinogenic, and optionally (b) a pharmaceutically acceptable excipient that aids in transporting the agent into the lesion, where it is preferably maintained for a sufficient period of time to negatively impact the lesion within the meaning of the present invention.

2. The method of claim 1, wherein said hyperproliferative lesion comprises at least one viral wart and said pharmaceutical composition comprises at least one agent comprising doxycycline or an analogue thereof.

3. The method of claim 1, wherein said local administration comprises intralesionally delivering said composition into the lesion.

4. The method of claim 1, wherein said local administration comprises topically applying said composition to the surface of the skin in the region of the lesion, and wherein said excipient aids in transporting the agent to the lesion, and preferably maintains the agent on the skin of the subject.

5. The method of claim 1, wherein said local administration comprises locally delivering said composition to the region or area in proximity to the lesion.

6. The method of claim 1, wherein the pharmaceutical composition comprises an agent comprising a chemotherapeutic agent, wherein (1) the agent interferes with DNA replication by topoisomerase inhibition; (2) the agent disrupts the microtubule and/or mitotic

spindle in a cell of the lesion; (3) the agent interferes with nucleotide synthesis or a combination thereof.

7. The method of claim 1, wherein the pharmaceutical composition comprises an agent selected from the group consisting of an antibiotic, a sclerosing agent and an antibiotic schlerosing agent.

8. The method of claim 1, wherein the pharmaceutical composition comprises at least one agent comprising tetracycline or an analogue thereof.

9. The method of claim 8, wherein the agent comprises doxycycline or an analogue thereof.

10. The method of claim 1, wherein the pharmaceutical composition comprises at least one agent selected from the group consisting of an immunomodulator, an immunoregulator, an immunosuppressant, an immunostimulant, and a non-steroidal anti-inflammatory agent.

11. The method of claim 1, wherein the pharmaceutical composition comprises at least one agent is selected from the group consisting of is an angiogenesis inhibitor, an agent that alters the structure, function, localization, or post-translational modification of small GTPases, a chemopreventative agent, an anti-fibrotic agent, an alkylphospholipid, an agent that targets apoptotic or anti-apopotic signaling, a nucleic acid-based therapeutic agent, and an agent that restores the function of a mutated gene

12. The method of claim 1, wherein the pharmaceutical composition comprises at least one agent selected from the group consisting of a protein kinase inhibitor, a lipid kinase inhibitor, a heat shock protein inhibitor, a protein chaperone inhibitor, a phosphatase inhibitor, a protease inhibitor and a combination thereof.

13. The method of claim 1, wherein the agent is selected from the group consisting of an alkylating agent, such as thiotepa or carboplatin; an anti-metabolite or a nucleoside analogue, such as triciribine, sangivamycin, or tubercidin;, a topoisomerase inhibitor, such as podophyllotoxin;, a microtubule inhibitor, such as mebendazole, a sclerosing agent, an antibiotic, such as doxycycline or analogues thereof; an anti-

inflammatory agent or a nonsteroidal anti-inflammatory agent (NSAID), such as celebrex; an agent that modulates gene transcription, such as a HDAC inhibitor comprising tricostatin A; a chemopreventative agent, such as a retinoid, such as fenretinide; an alkylphospholipid, such as miltefosine; a HSP90 inhibitor, such as geldanamycin derivatives, such as 17-AAG, radicicol or analogues thereof; halofuginone, gentamicin, rapamycin, and a combination thereof.

14. The method of claim 1, wherein the excipient comprises at least one of a skin penetrant and an analgesic.

15. The method of claim 1, wherein the excipient comprises a powder, a liquid solution or suspension, a cream, a lotion, a gel, or a skin penetrant.

16. A composition useful for locally treating at least one hyperproliferative lesion selected from the group consisting of a viral wart, a basal cell carcinoma (BCC), actinic keratosis (AK), a squamous cell carcinoma (SCC), a melanoma, a pre-neoplastic lesion (e.g. nevi), a skin metastases of other tumors/cancers (e.g. cutaneous T cell lymphomas, skin lesions of Kaposi's sarcoma and a cutaneous or subcutaneous hamartomas, such as neurofibroma (e.g. dermal neurofibroma, subdermal neurofibroma or superficial plexiform neurofibroma) in a subject in need of such treatment, which composition comprises (a) at least one agent for abating the negative impact of the lesion on the subject, wherein the agent is non-carcinogenic, and optionally (b) a pharmaceutically acceptable excipient for local delivery to include topical, intralesional or general delivery to the tissue surrounding the lesion that aids in transporting the agent into the lesion, and preferably maintains the agent on the subject's skin for a period of time.

17. The composition of claim 16, wherein the pharmaceutical composition comprises at least one agent comprising is a chemotherapeutic agent, wherein (1) the agent interferes with DNA replication by topoisomerase inhibition; .(2) the agent disrupts the microtubule and/or mitotic spindle; (3) the agent interferes with nucleotide synthesis or a combination thereof.

18. The composition of claim 16, wherein the pharmaceutical composition comprises an agent selected from the group consisting of an antibiotic, a sclerosing agent and an antibiotic schlerosing agent.

19. The composition of claim 16, wherein the pharmaceutical composition comprises at least one agent comprising tetracycline or an analogue thereof.

20. The composition of claim 19, wherein the agent comprises doxycycline or an analogue thereof.

21. The composition of claim 16, wherein the pharmaceutical composition comprises at least one agent selected from the group consisting of an immunomodulator, an immunoregulator, an immunosuppressant, an immunostimulant, and a non-steroidal anti-inflammatory agent.

22. The composition of claim 16, wherein the pharmaceutical composition comprises at least one agent is selected from the group consisting of is an angiogenesis inhibitor, an agent that alters the structure, function, localization, or post-translational modification of small GTPases, a chemopreventative agent, an anti-fibrotic agent, an alkylphospholipid, an agent that targets apoptotic or anti-apopotic signaling, a nucleic acid-based therapeutic agent, and an agent that restores the function of a mutated gene

23. The composition of claim 16, wherein the pharmaceutical composition comprises at least one agent selected from the group consisting of a protein kinase inhibitor, a lipid kinase inhibitor, a heat shock protein inhibitor, a protein chaperone inhibitor, a phosphatase inhibitor, a protease inhibitor and a combination thereof.

24. The composition of claim 16, wherein the agent is selected from the group consisting of an alkylating agent, such as thiotepa or carboplatin; an anti-metabolite or a nucleoside analogue, such as triciribine, sangivamycin, or tubercidin;, a topoisomerase inhibitor, such as podophyllotoxin;, a microtubule inhibitor, such as mebendazole, a sclerosing agent, an antibiotic, such as doxycycline or analogues thereof; an anti-inflammatory agent or a nonsteroidal anti-inflammatory agent (NSAID), such as celebrex; an agent that modulates gene transcription, such as a HDAC inhibitor comprising tricostatin A; a chemopreventative agent, such as a retinoid, such as fenretinide; an alkylphospholipid, such as miltefosine; a HSP90 inhibitor, such as geldanamycin derivatives, such as 17-AAG, radicicol or analogues thereof; halofuginone, gentamicin, rapamycin, and a combination thereof.

25. The composition of claim 16, wherein the excipient comprises at least one of a skin penetrant and an analgesic.

26. The composition of claim 16, wherein the excipient comprises a powder, a liquid solution or suspension, a cream, a lotion, a gel, or a skin penetrant.