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(71) Applicant: **HPVVAX, LLC** [US/US]; 140 SW Chamber Court, Suite 200, Port St. Lucie, FL 34986 (US).

(72) Inventor: **IOANNIDES, Tim**; 140 SW Chamber Court, Suite 200, Port St. Lucie, FL 34986 (US).

(74) Agent: **WHITLOCK, Ted**; 5323 SW 38th Avenue, Fort Lauderdale, FL 33312 (US).

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(54) Title: METHOD AND COMPOSITION FOR TREATING CANCER OR SKIN LESION USING A VACCINE

(57) Abstract: A method for treating or reducing the incidence of recurrence of cancer, benign tumors or HPV-associated lesions, including skin cancer, and particularly squamous cell carcinoma (SCC) and basal-cell carcinoma, by administering one or more doses of HPV recombinant vaccine to a patient.

METHOD AND COMPOSITION FOR TREATING CANCER OR SKIN LESION USING A VACCINE

FIELD OF THE INVENTION

[0001] The invention relates to treating cancer, including skin cancer or benign or malignant tumor and, more particularly, to a method for treatment, or reducing the incidence of recurrence, of cancer or tumors comprising administration of a vaccine, including local administration of a composition comprising the vaccine as a therapeutic agent.

BACKGROUND OF THE INVENTION

[0002] Skin cancer consists of three main types, namely, basal-cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma, and is the most common form of cancer globally. Understandably, there have been ongoing studies for many years searching for effective methods to treat, and possibly cure, these types of skin cancer.

[0003] It is generally accepted that human papillomavirus (HPV) is associated with causing certain types of skin cancer, particularly squamous cell carcinoma (SCC). HPV is a DNA virus that can infect certain types of tissues in humans. There are upwards of thirty subtypes of HPV and some of these subtypes have been associated with cervical cancer, including HPV16 and HPV18. HPV is not known to be a cause or to be associated with basal cell carcinoma (BCC) or melanoma.

[0004] Vaccines have been developed and shown to prevent cervical cancer in women and other conditions caused by or associated with HPV infection. GARDASIL® is a commercially available vaccine having activity against HPV (types 6, 11, 16, and 18).

[0005] GARDASIL® 9 is another commercially available vaccine marketed for prevention of HPV (types 16, 18, 31, 33, 45, 52, and 58). GARDASIL® is indicated for use in girls and boys from ages 9-26; GARDASIL® 9 is also indicated for use in girls from ages 9-26, and in boys from ages 9-15.

[0006] Other vaccines have been produced, as well, for treating subtypes of HPV, particularly HPV16 and HPV18. GARDASIL® and other known vaccines administered prophylactically, to prevent certain HPV infections and associated cancers, are referred to herein as "preventive vaccines." These preventive vaccines are typically administered for systemic action, being injected into a patient subcutaneously or intramuscularly (e.g., deltoid), remote from any particular target, such as the cervix. Moreover, they are generally accepted to be effective prior to exposure to HPV and are not commonly known to be effective for treatment after exposure to, or infection with, HPV.

[0007] Other preventive vaccines include, for example, an improved vaccine composition as described in Chinese Pat App. No. 101890160 (CN'160) comprising certain L1 proteins of HPV (as in GARDASIL®), and additional HPV-specific components. Preventive vaccines comprising HPV-type 16 and 18 proteins are also suggested to provide cross-protection against other HPV types, as described in US Pub. No. 2005/0287161.

[0008] Vaccines used for treatment (referred to herein as "therapeutic vaccines") are described. However, these therapeutic vaccines require more than viral-specific components,

such as HPV L1 proteins that comprise the commercially available preventive vaccines, such as GARDASIL®.

[0009] US Pub. No. 2007/0218074 describes the use of a vaccine composition comprising host-cell peptides from an HPV-infected cell. The host-cell peptides, e.g., the early antigens, E6 or E7, that present on the surface of cells infected with HPV, are fragments of host-cell proteins. The criticality of the polypeptides E6 or E7 in a vaccine used in treating certain cancer types is described in *Development of HPV vaccines for HPV-associated head and neck squamous cell Carcinoma,* Devaraj, et al., Crit Rev Oral Biol Med. 2003;14(5):345-62. Another vaccine which includes a host-cell protein (BAX) is described in US Pat. No. 8,399,610.

[00010] Yet another vaccine composition comprising other or additional antigens in combination with HPV-16 peptides, is a vaccine composition described in US Pub. No. 2011//0070252 which additionally requires Trojan antigen.

[00011] US Pub. No. 2011/0110979 (US '979) and US Pub. No. 2012/0288538 (US '538) disclose therapeutic use of an HPV vaccine comprising E6 or E7 polypeptides (peptide fragments from host cells infected with HPV). US '538 describes that E6 and E7 are crucial to induce transformation into HPV-infected cells, and states that a vaccine composition which does not include E6 or E7 would not be expected to work on cells that do not have E6 or E7, i.e., cells such as BCC that are not infected with HPV. The method described in the US'979 publication additionally requires an immunostimulant or adjuvant.

[00012] Although the US '979 and US '538 publications describe the use of therapeutic vaccines against skin cancers, such as SCC or epithelial SCC, they do not describe use of the

vaccine against other skin cancers, such as BCC or melanoma, likely based on the understanding that BCC and melanoma are not associated with HPV infection.

[00013] The limitations and disadvantages of the above uses of vaccines can be overcome by the use of a method in accordance with the subject invention. There is a need in the medical and health fields for safe and efficacious cancer treatments, including skin cancers or cancers that are typically not associated with HPV infection, which are convenient for the patient as well as the health practitioner.

SUMMARY OF THE INVENTION

[00015] The subject invention concerns a method for treating a patient having skin cancer, benign or malignant tumor, whether or not associated with or related to human papilloma virus (HPV) infection, or other skin lesion, said method comprising the steps of:

administering to a patient having or in need of treatment of a tumor, cancer or other skin lesion, a therapeutically effective dose of a commercially available HPV vaccine. The vaccine can be administered directly to the cancer or lesion, either by direct application onto (topical) the tumor or lesion, or by direct injection into the tumor or lesion. Alternatively, the vaccine can be administered for therapeutic use by systemic injection. A method of treatment according to the subject invention can also include any combination of topical application, direct or systemic injection. A therapeutically effective dose can be a conventional, approved dose of the vaccine per its label indication.

[00016] In one embodiment, the method can comprise:

a) administering to a patient 27 years of age or older or a patient previously not immunized with an HPV vaccine, a first dose of an HPV vaccine which is free of host-cell peptide, polypeptide, or protein or a degradant product thereof;

b) administering to the patient a second dose of the HPV vaccine about one month to about three months after the first administration; and

c) optionally, administering to the patient a third dose of the HPV vaccine about five months to about seven months after the first dose.

[00015] Following the initial, conventional administration of the vaccine according to step a), above, the second or third administrations according to steps b) and c), above, can be by injection, or can be by topical administration of a composition comprising the vaccine. Alternatively, the second or third administrations of steps b) or c) can include both injection and by topical administration.

[00016] In one embodiment, the second dose of HPV vaccine is administered about two months after administering the first dose and the third dose of HPV vaccine is administered about six months after administering the first dose.

[00017] The HPV vaccine can be selected from HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine comprising HPV L1 proteins and HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine comprising HPV L1 proteins, and preferably is free or substantially free of host-cell early antigen, e.g., E6 or E7.

[00018] In one preferred embodiment, the method does not comprise or is without administering an additional or other immunostimulant or adjuvant.

[00019] In one preferred embodiment, the method comprises administering an additional or other immunomodulatory agent, such as an immunostimulant or adjuvant.

[00020] By carrying out the method, the size of the cancer or HPV-related lesion can be substantially reduced, or completely eliminated. In addition, the incidence of recurrence of the cancer or HPV-related lesion can be reduced. The method can be effective in treating or reducing the incidence of recurrence of a cancer, benign tumor, or HPV-related lesion such as

squamous cell carcinoma, basal cell carcinoma, melanoma, verruca vulgaris, or condyloma accuminata.

[00021] In one embodiment, the method can comprise a single dose of the vaccine. For example, a single dose of the vaccine can be administered topically, or by injection directly into a tumor or systemically to reduce the size or eliminate the tumor. A physician or healthcare professional can administer a second or subsequent dose, as needed or as determined by the physician or healthcare professional.

[00022] In one embodiment, the patient in need of treatment can be a person previously immunized with the vaccine. In another embodiment, the patient in need of treatment can be a person that has not been previously immunized with the vaccine.

[00023] Each dose of HPV vaccine administered in the above method steps is preferably about 0.5 ml, and is more preferably 0.5 ml.

[00024] The method can further comprise establishing a positive diagnosis of cancer, benign tumor, or HPV infection prior to administering the first dose of HPV vaccine.

[00025] An alternative embodiment of the method according to the subject invention comprises treating a patient having cancer, benign tumor, or a human papilloma virus-related (HPV-related) lesion, wherein the method comprises administering a dose of an HPV vaccine directly to the cancer, tumor, or lesion or an area immediately surrounding the tumor or lesion.

[00026] This alternative embodiment of the method according to the subject invention can further comprise the steps of:

administering a second dose of the HPV vaccine directly to the tumor or lesion or an area immediately surrounding the tumor or lesion about one month to about three months after administering the first dose; and

optionally, administering a third dose of the HPV vaccine directly to the tumor or lesion or an area immediately surrounding the tumor or lesion about five months to about seven months after administering the first dose.

[00027] These direct second or third administrations of a composition comprising the vaccine can be topical applications, or can be by injection into the lesion.

[00028] In this alternative embodiment of the subject method, the second dose of HPV vaccine can be administered about two months after administering the first dose and the third dose of HPV vaccine can be administered about six months after administering the first dose.

[00029] By carrying out the alternative embodiment of the method according to the subject invention, the size of the cancer, tumor, or HPV-related lesion can be substantially reduced or completely eliminated. In addition, the incidence of recurrence of the cancer, tumor, or HPV-related lesion can be reduced.

[00030] The preferred dose of each subsequent administration of HPV vaccine, if any, is 0.5 ml.

[00031] The method according to any embodiment of the invention can be used for treating cancer, benign tumor, or HPV-related lesion, including, but not limited to, a benign

tumor associated or unassociated with HPV infection, squamous cell carcinoma, basal cell carcinoma, melanoma, verruca vulgaris, and condyloma accuminata.

[00032] The method can further comprise establishing a positive diagnosis of cancer, benign tumor, or HPV infection prior to administering the first dose of HPV vaccine.

[00033] In one preferred embodiment, the direct or local administration of the vaccine is administered by injection, and more preferably the method does not comprise administering an additional or other immunostimulant or adjuvant, with, during or following the administration of the vaccine.

[00034] Alternatively, the subject method can comprise administering an additional or other immunomodulatory agent, e.g., and immunostimulant or adjuvant, with, during or following the administration of the vaccine.

[00035] In another preferred embodiment, the vaccine can be formulated for topical administration and applied directly to the lesion in the form of a topical solution or suspension, such as a liquid or spray, gel, cream, salve, ointment, foam or mousse, or the like.

[00036] The subject invention can particularly concern a method for treating a tumor wherein the method comprises administering at least one dose of a commercially available HPV vaccine to a patient having a tumor. Advantageously, the subject method has been found to be effective for treating a tumor in glandular tissue, such as breast, pituitary (e.g., invasive pituitary adenoma), prostate, or pancreas. This embodiment can include at administering at least one dose of the vaccine directly into the tumor, itself.

[00037] The subject invention can comprise administering at least one dose of the vaccine systemically, e.g., by intramuscular (IM) injection, alone, or in combination with (concomitantly or shortly before or after) the direct administration of the vaccine to the tumor.

[00038] Alternatively, in certain instances, e.g., when the tumor presents on or near the surface of the body, this method can further comprise topical administration of at least one dose of the HPV vaccine, alone, or in combination with direct injection into the tumor or in combination with systemic injection, or in combination with both direct and systemic injection.

[00039] Compositions comprising the vaccine are also included as part of the invention. For example, the HPV vaccine can be formulated with one or more additional active pharmaceutical ingredients for administration to the patient. Additional active pharmaceutical ingredients can be one or more immunomodulatory agent for modulating the effect of the vaccine, or one or more local anesthetic agent, e.g., lidocaine (with or without epinephrine), for reducing patient discomfort during the injection.

[00040] One example of a composition of the invention comprises a 1:1 (v/v) ratio mixture of 0.5 ml of a commercially available HPV vaccine and 0.5 ml of a commercially available lidocaine solution (e.g., 0.5% (w/v), 1% (w/v), or 2% (w/v)). The composition can be thoroughly mixed and injected into a patient for treatment. Ratios ranging from 1:10 (v/v) vaccine:anesthetic solution to 10:1 (v/v) vaccine:anesthetic solution can be used, as would be understood in the art.

[00041] The HPV vaccine can also be formulated with one or more excipients or diluents for administration to the patient. Excipients and diluents can include one or more conventional pharmaceutically acceptable ingredients useful for formulating topical preparations, including

but not limited to a bases for preparing a cream, emollient, gel, lotion, salve, or the like, and can optionally include penetration enhancers, preservatives, release-controlling agents, solubilizers, stabilizers, thickeners or thinners, or the like.

[00042] Solutions for injection can also include one or more buffer, emollient, diluent, pH adjuster, preservative, solubilizer, stabilizer, or the like.

[00043] These compositions can be prepared as a manufactured product which can be shipped, stored, and used as needed, including a later time, or can be compounded at the point of care or remotely for immediate single-use treatment.

[00044] A composition of the invention can include one or more additional active pharmaceutical ingredient without an excipient or diluent, or can include one or more active pharmaceutical ingredient and one or more excipient or diluent.

[00045] A composition of the invention can include one or more excipient or diluent without an additional active pharmaceutical ingredient, or can include one or more excipient or diluent and one or more active pharmaceutical ingredient.

[00046] To the knowledge of the inventor, administration of HPV vaccines comprising only HPV antigens (being free of host-cell peptides), to a previously unimmunized patient, or an adult patient aged 27 or greater, to eliminate or reduce the incidence of recurrence of skin cancer, benign or malignant tumor or other skin lesion that is not an HPV-associated lesion, has not been previously described. Nor has the direct or local administration of a vaccine by topical application or by direct injection into the lesion or tumor been previously described to eliminate the lesion and reduce the incidence of its recurrence.

DETAILED DESCRIPTION

[00047] The present invention is directed to a method of treating cancer, benign tumor, skin cancer, such as squamous cell carcinoma (SCC), or a skin lesion associated with or unassociated with human papilloma virus (HPV) infection, and includes treating a tumor originating in glandular tissue, such as breast, pituitary, prostate, or pancreatic tissue. One embodiment of a method in accordance with the subject invention comprises the administration of a commercially available HPV vaccine, such as an HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine, to a patient having a cancer or tumor.

[00048] In one preferred embodiment, the subject method comprises administering at least one dose of the HPV vaccine to a patent that has not been previously immunized with an HPV vaccine, or to an adult patient aged 27 or older. For purposes of the subject invention, a patient previously not immunized with an HPV vaccine is termed an "unimmunized patient" regardless of other immunizations the patient may have received against other conditions or diseases.

[00049] The dosing regimen can be a single administration by direct injection, systemic injection, or topical application, or a combination of any of these administration routes. Alternatively, the subject method can comprise multiple (more than one) administration, or multiple (concomitant) administrations by direct injection, systemic injection or topical application of the vaccine.

[00050] The subject method can also comprise administering in accordance with the conventionally accepted dosing series for a vaccine. For example, HPV vaccines are typically administered using a dosing regimen comprising a first dose, a second dose about two months

following the first dose, and a third dose about six months following the first dose. These second, third, or subsequent administrations can be systemic injection, e.g., conventional intramuscular injection, or can be direct administration to the lesion by intralesional injection or by topical administration.

[00051] The method embodiments of the present invention have surprisingly been found to have beneficial results in treating, or minimizing the occurrence, recurrence, and/or progression of, cancer lesions or benign tumors that are not associated with HPV infection, such as basal-cell carcinoma (BBC) or melanoma.

[00052] While not being limited to any particular theory, it is proposed that the subject method can increase, i.e. boost a patient's immune response that may manifest clinically as increased surveillance in skin cells to decrease the likelihood of development and progression of abnormal skin cells that produce the skin cancer, particularly, but not exclusively, SCC.

[00053] Alternatively, the method of the invention can interfere with inherent functional activities of viral and virus-like proteins by other mechanisms. This interference would include the complete or partial functional inactivation of viral and virus-like materials altered or activated by exogenous and/or environmental agents such as ultraviolet light.

[00054] As used herein, the terms "HPV" and "human papillomavirus" refer to a non-enveloped, double-stranded DNA viruses of the papillomavirus family. Their genomes are circular and approximately 8 kilobase pairs in size. Most HPVs encode eight major proteins, six located in the "early" region (E1-E2) and two in the "late" region (L1 (the major capsid protein) and L2 (the minor capsid protein)). Over 120 HPV types have been identified, and they are designated by numbers (e.g., HPV-16, HPV-18, etc.).

[00055] In one embodiment, an HPV vaccine of the subject invention comprises one or more proteins (e.g., a recombinant L1 protein) from one, two, three, four, five, six, seven, eight, nine, ten or more different HPV types. Methods of expressing HPV L1 proteins and methods of making HPV vaccines are known in the art and described in, e.g., U.S. Patent Nos. 5,820,870 and 6,251,678, which are incorporated herein by reference in their entireties for all purposes.

[00056] In one embodiment, the HPV vaccine employed in the subject method contains purified inactive viral or virus-like proteins, such as the commercially available GARDASIL®, which is an HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine or GARDASIL® 9, an HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine. In another embodiment, the HPV vaccine is the commercially available CERVARIX®, which is an HPV bivalent (types 16 and 18) recombinant vaccine. A vaccine useful in accordance with this embodiment of the subject method is preferably free of host-cell and/or non-L1 HPV peptide, polypeptide, or protein, such as the early antigens, E6 or E7, which are fragments of host-cell peptides that present on the surface of an HPV-infected cell.

[00057] The vaccine can be administered for treating cancerous or benign tumors, including cancer lesions not associated with HPV infection, cancer (tumors or lesions) associated with HPV infection, benign tumors not associated with HPV infection, or non-cancerous HPV-related lesions in an unimmunized patient.

[00058] Alternatively, the vaccine can be administered to reduce the incidence of recurrence of cancer, a benign tumor, or an HPV-related lesion in an unimmunized patient. In another embodiment, the vaccine can be administered to treat cancer, benign tumor, or an HPV-

related lesion, or reduce the incidence of recurrence thereof, in an adult patient aged 27 or greater.

[00059] More particularly, one preferred embodiment of the invention comprises a method for the treatment of cancer, benign tumor or HPV-related lesion, in a patient that is unimmunized, or an adult patient aged 27 or older, comprising the steps of:

i. administering to the patient a first dose of an HPV recombinant vaccine free of host-cell peptides, polypeptides or proteins;

ii. administering to the patient a second dose of the HPV recombinant vaccine free of host-cell peptides, polypeptides or proteins between about one month and about three months after the first dose; and

iii. optionally, administering to the patient a third dose of the HPV vaccine free of host-cell peptides, polypeptides or proteins between about five months to about seven months after administering the first dose.

[00060] The second or third, or subsequent, administration of the vaccine dose can be systemic, e.g., intramuscular injection, or can be by direct administration to the lesion. The direct administration of the vaccine composition to the lesion can be by intralesional injection, or can be applied topically to the lesion. In a further embodiment, second, third or subsequent administrations are both systemic and by direct application of vaccine to the lesion. Such direct administration to the lesion can be intralesional injection or by topical application of a vaccine composition formulated for topical administration.

[00061] It would be understood by medical practitioners that the reference to the timing of subsequent administrations of the vaccine is approximate and can vary by days or even weeks.

This variation can result from patient compliance or non-compliance to the scheduled dosing, clinical observation by the treating physician who may decide to advance (for more aggressive treatment) or delay a subsequent administration for medical reasons. Generally, however, an effective result can be achieved by following a dosing schedule where the second dose is administered about two months following the first dose, and a third dose at about six months after the first dose. Additional (fourth, or fifth) doses can be administered if the physician deems that subsequent administrations can provide benefit to the patient.

[00062] A typical total dose for each administration according to the method of the subject invention is about 0.5 ml of the vaccine, and is preferably 0.5 ml of a commercially available HPV vaccine.

[00063] The terms "cancer," "cancerous," or "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma)

colorectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease,

non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In another embodiment, the cancer is carcinoma, lymphoma, leukemia, blastoma, and sarcoma. More particular examples of such cancers include squamous cell carcinoma, myeloma, small-cell lung cancer, non-small cell lung cancer, glioma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute myeloid leukemia (AML), multiple myeloma, gastrointestinal (tract) cancer, renal cancer, ovarian cancer, liver cancer, lymphoblastic leukemia, lymphocytic leukemia, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, melanoma, chondrosarcoma, neuroblastoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, brain cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. In certain exemplary embodiments, a cancer is an HPV-associated cancer.

[00064] A particular example of cancer includes skin cancer, e.g., basal cell carcinoma and/or squamous cell carcinoma, among other known skin cancers. Another example of cancer includes breast cancer. Yet another example of cancer includes prostate cancer. Yet another example includes penile cancer. Yet another example of cancer includes ovarian, cervical, vaginal and/or vulvar cancer. Yet another example of cancer includes bladder cancer. Yet another example of cancer includes colorectal and/or anal cancer. Yet another example of cancer includes oropharyngeal cancer (e.g., cancer of the throat, soft palate, base of tongue, adenoids and/or tonsils). Yet another example of cancer includes renal cancer. Yet another example of cancer includes liver cancer.

[00065] In certain exemplary embodiments, a cancer is associated with decreased expression of Bcl-2-associated X protein (BAX) and/or Bcl-2 homologous antagonist/killer (BAK1). In other exemplary embodiments, a cancer is associated with one or more aberrant mitochondrial activities. In certain exemplary embodiments, an HPV vaccine of the invention increases BAX and/or BAK1 expression in a tumor cell and/or promotes apoptosis of the tumor cell. In other aspects, the combination of vitamin D and an HPV vaccine of the invention increases BAX and/or BAK1 expression in a tumor cell and/or promotes apoptosis of a tumor cell. In another embodiment, an HPV vaccine of the invention modulates one or more mitochondrial activities in a tumor cell.

[00066] The above embodiments of a method of treatment according to the subject invention can be efficacious for treating skin cancer in the patient, and particularly squamous cell carcinoma, wherein a skin cancer lesion is reduced in size or eliminated following the three administrations of the vaccine.

[00067] The treatment method in accordance with the subject invention can also reduce the incidence of recurrence of benign tumors or cancer tumors or lesions, including skin cancer, in the patient.

[00068] In particular the treatment method according to the subject invention comprises eliminating, or reducing the size or incidence of recurrence of a cancerous tumor of the breast, eliminating, or reducing the size or incidence of recurrence in a cancerous tumor of the prostate, eliminating, or reducing the size or incidence of recurrence of a cancerous tumor of the pancreas, or eliminating, or reducing the size or incidence of recurrence of a cancerous tumor of the pituitary gland, e.g., invasive pituitary adenoma.

[00069] Other particular types of cancers or tumors that can benefit from treatment using an HPV vaccine in accordance with the method of the subject invention include, and are not limited to, cervical cancer, anal cancer, oropharyngeal cancers (throat, soft palate, base of tongue, or tonsils), vaginal cancer, vulvar cancer, penile cancer, colorectal cancer, bladder cancer, lung cancer, renal cancer, liver cancer, ovarian cancer, pancreatic mucinous cystic neoplasms, gastric or stomach cancer.

[00070] The method according to the subject invention can also be effective to reduce the size or eliminate an HPV-associated, but non-cancerous, lesion, such as warts, including genital warts, e.g., verruca vulgaris or condyloma accuminata

[00071] It is a further unexpected result of the present invention to provide a method of reducing the incidence of recurrence of skin cancer, and particularly squamous cell carcinoma following administration of one or more injections of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine, wherein the vaccine is substantially free of host-cell peptides, polypeptides, or proteins which, as a result of HPV infection of the cell, present on the surface of the infected cell. Further unexpected results of the subject method of treatment comprise reducing the size of, eliminating, or reducing the incidence of recurrence of skin lesions that are not associated with HPV infection, such as basal cell carcinoma or melanoma.

[00072] The invention pertains to uses of the above-described agents for the therapeutic treatment of cancer. Accordingly, an HPV vaccine composition of the present invention is incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise an HPV viral or viral-like protein and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and

all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00073] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous (IV), intradermal, subcutaneous (SC or SQ), intraperitoneal, intramuscular, oral (e.g., inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00074] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable

carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, orby the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00075] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00076] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier to be swallowed or ingested as a solution or suspension, or for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00077] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[00078] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or

suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00079] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00080] In one embodiment, the HPV viral or viral-like proteins are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00081] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be

achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[00082] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit large therapeutic indices are preferred. Although compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[00083] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the EC50 (i.e., the concentration of the test compound which achieves a half-maximal response) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[00084] The pharmaceutical compositions can be included in a container, pack or dispenser together with optional instructions for administration.

[00085] The route of delivery can be dependent on the disorder of the patient. In certain exemplary embodiments, a subject diagnosed with skin cancer can be administered an HPV vaccine composition of the invention by topical administration. In addition to an HPV vaccine compositions of the invention, a patient can be administered a second therapy, e.g., a palliative therapy and/or disease-specific therapy. The secondary therapy can be, for example, symptomatic (e.g., for alleviating symptoms), protective (e.g., for slowing or halting disease progression), or restorative (e.g., for reversing the disease process). For the treatment of cancer, for example, symptomatic therapies can further include another chemotherapeutic agent used as a combination therapy as described further herein.

[00086] In general, an HPV vaccine composition of the invention can be administered by any suitable method. As used herein, topical delivery can refer to the direct application of an HPV vaccine composition to any surface of the body, including the eye, a mucous membrane, surfaces of a body cavity, or to any internal surface. Formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, sprays, and liquids. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Topical administration can also be used as a means to selectively deliver an HPV vaccine composition to the epidermis or dermis of a subject, or to specific strata thereof, or to an underlying tissue.

[00087] Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives. Intraventricular injection

may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

[00088] An HPV vaccine composition of the invention can be administered to a subject by pulmonary delivery. Pulmonary delivery compositions can be delivered by inhalation of a dispersion so that the composition within the dispersion can reach the lung where it can be readily absorbed through the alveolar region directly into blood circulation. Pulmonary delivery can be effective both for systemic delivery and for localized delivery to treat diseases of the lungs.

[00089] Pulmonary delivery can be achieved by different approaches, including the use of nebulized, aerosolized, micellular and dry powder-based formulations. Delivery can be achieved with liquid nebulizers, aerosol-based inhalers, and dry powder dispersion devices. Metered-dose devices are preferred. One of the benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self-contained. Dry powder dispersion devices, for example, deliver drugs that may be readily formulated as dry powders. An HPV vaccine composition may be stably stored as lyophilized or spray-dried powders by itself or in combination with suitable powder carriers. The delivery of a composition for inhalation can be mediated by a dosing timing element which can include a timer, a dose counter, time measuring device, or a time indicator which when incorporated into the device enables dose tracking, compliance monitoring, and/or dose triggering to a patient during administration of the aerosol medicament.

[00090] The types of pharmaceutical excipients that are useful as carriers include stabilizers such as Human Serum Albumin (HSA), bulking agents such as carbohydrates, amino acids and polypeptides; pH adjusters or buffers; salts such as sodium chloride; and the like. These carriers may be in a crystalline or amorphous form or may be a mixture of the two.

[00091] Bulking agents that are particularly valuable include compatible carbohydrates, polypeptides, amino acids or combinations thereof. Suitable carbohydrates include monosaccharides such as galactose, D-mannose, sorbose, and the like; disaccharides, such as lactose, trehalose, and the like; cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin; and polysaccharides, such as raffinose, maltodextrins, dextrans, and the like; alditols, such as mannitol, xylitol, and the like. A preferred group of carbohydrates includes lactose, trehalose, raffinose maltodextrins, and mannitol. Suitable polypeptides include aspartame. Amino acids include alanine and glycine, with glycine being preferred.

[00092] Suitable pH adjusters or buffers include organic salts prepared from organic acids and bases, such as sodium citrate, sodium ascorbate, and the like; sodium citrate is preferred.

[00093] One or more HPV viral or viral-like proteins of the invention (i.e., an HPV vaccine) can be administered by oral or nasal delivery. For example, drugs administered through these membranes have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the drug to the hostile gastrointestinal (GI) environment. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized and removed easily.

[00094] Another embodiment in accordance with the subject invention comprises administering an HPV vaccine administered to a patient by direct or local administration, e.g., injection, into a skin lesion or surrounding area of the lesion. This direct administration method can be useful in patients suffering from cancer, particularly skin cancer. This embodiment of the method can also be useful for treating non-cancerous (benign) tumors, or non-cancerous lesions associated with HPV, such as warts, e.g., verruca vulgaris or condyloma accuminata.

[00095] In an embodiment comprising direct injection into or surrounding a lesion, the dosing regimen can comprise a single administration or more than one administration. For example, a three-administration dosing series, as above, can be followed. Alternatively, a physician can administer a subsequent dose as needed (prn) following an initial dose directly into or surrounding the lesion. Divided dosing of the vaccine for any particular single time point is considered to be a single administration.

[00096] This direct-administration embodiment of the invention can have beneficial results in treating, or minimizing the occurrence, recurrence, and/or progression of, cancer lesions or tumors such as basal-cell carcinoma (BBC) or melanoma, or non-cancerous (benign) tumors that are not associated with HPV infection.

[00097] In one embodiment of the subject invention, the method is carried out without the administration of an additional or other immunostimulant or adjuvant either with, during, or following the treatment method of the invention.

[00098] Alternatively, the subject method can comprise administering an additional or other immunomodulatory agent, e.g., and immunostimulant or adjuvant, with, during or

following the administration of the vaccine. Non-limiting examples of immunomodulatory agents useful as part of the subject method include:

1) Vitamin D and its analogues;
2) Sirolimus;
3) Interferon and its analogues;
4) Vitamin A and its analogues, e.g., Soriatane (a retinoid)
5) Imiquimod;
6) Ingenol mebutate; and
7) T4 endonuclease
8) Antimetabolites, e.g. 5 Fluorouracil, Methotrexate
9) Cyclooxygenase inhibitors, e.g. Diclofenac

[00099] These agents can be given in combination locally or systemically with, or contemporaneous with, the HPV vaccine as described herein, to enhance the effect of the treatment. For example, in a previously HPV immunized patient having a tumor (skin, lung, or the like), a combination of interferon and HPV antigen vaccine could be given locally. Interferon may or may not also be given at the same time systemically. This administration can enhance local destruction of the tumor or other lesion without the systemic side effects associated with interferon.

[000100] In another aspect of the invention, the invention provides a method for treating cancer in an individual comprising administering to the individual a combination therapy which comprises an HPV vaccine and one or more additional chemotherapeutic agents other than the HPV vaccine. The specific dosage and dosage schedule of the additional therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific therapeutic agent that is being used.

[000101] Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziri dines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; cally statin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); eleutherobin; pancrati statin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, especially calicheamicin gammall and calicheamicin phill, see, e.g., Agnew, Chem. Intl. Ed. Engl., 33 : 183-186 (1994); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin,

quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP- 16); ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylormthine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included are anti-hormonal agents that act to regulate or inhibit hormone action

on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestane, fadrozole, vorozole, letrozole, and anastrozole; and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[000102] Each therapeutic agent in a combination therapy of the invention may be administered either alone or in a medicament (also referred to herein as a pharmaceutical composition) which comprises the therapeutic agent and one or more pharmaceutically acceptable carriers, excipients and diluents, according to standard pharmaceutical practice.

[000103] Each therapeutic agent in a combination therapy of the invention may be administered simultaneously (i.e., in the same medicament), concurrently (i.e., in separate medicaments administered one right after the other in any order) or sequentially in any order. Sequential administration is particularly useful when the therapeutic agents in the combination therapy are in different dosage forms (one agent is a tablet or capsule and another agent is a sterile liquid) and/or are administered on different dosing schedules, e.g., a chemotherapeutic that is administered at least daily and an HPV vaccine that is administered less frequently, such as once weekly, once every two weeks, or once every three weeks.

[000104] In some embodiments, the HPV vaccine is administered before administration of the chemotherapeutic agent, while in other embodiments, the HPV vaccine is administered after

administration of the chemotherapeutic agent. In another embodiment, the HPV vaccine is administered concurrently with the chemotherapeutic agent.

[000105] In some embodiments, at least one of the therapeutic agents in the combination therapy is administered using the same dosage regimen (dose, frequency and duration of treatment) that is typically employed when the agent is used as monotherapy for treating the same cancer. In other embodiments, the patient receives a lower total amount of at least one of the therapeutic agents in the combination therapy than when the agent is used as monotherapy, e.g., smaller doses, less frequent doses, and/or shorter treatment duration.

[000106] Each therapeutic agent in a combination therapy of the invention can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, topical, and transdermal routes of administration.

[000107] A combination therapy of the invention may be used prior to or following surgery to remove a tumor and may be used prior to, during or after radiation therapy.

[000108] In some embodiments, a combination therapy of the invention is administered to a patient who has not been previously treated with a biotherapeutic or chemotherapeutic agent, i.e., is treatment-naive. In other embodiments, the combination therapy is administered to a patient who failed to achieve a sustained response after prior therapy with a biotherapeutic or chemotherapeutic agent, i.e., is treatment-experienced.

[000109] A combination therapy of the invention is typically used to treat a tumor that is large enough to be found by palpation, visual observation or by imaging techniques well known in the art, such as MRI, ultrasound, or CAT scan.

[000110] Any commercially available HPV vaccine can be employed for administration directly to a cancer or HPV-related lesion. For example, this embodiment of the subject method can comprise directly administering into or surrounding a lesion, a vaccine comprising purified inactive viral or virus-like proteins, such as the commercially available GARDASIL®, which is an HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine or GARDASIL® 9, an HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine or CERVARIX®, an HPV bivalent (types 16 and 18) recombinant vaccine.

[000111] A vaccine useful in accordance with this embodiment of the subject method can include host-cell peptides, polypeptides, or proteins, such as the early antigens, E6 or E7 or exclude or be free of host-cell peptides, polypeptides, or proteins, such as the early antigens, E6 or E7. The vaccine can be administered for treating cancer, a benign tumor, or HPV-related lesion in a patient of any age, whether an unimmunized patient or a patient previously immunized with an HPV vaccine.

[000112] The vaccine can be directly or locally administered into or surrounding a lesion or tumor to reduce the incidence of recurrence of cancer, benign tumor, or an HPV-related lesion in a patient.

[000113] In another embodiment, the vaccine can be administered to treat cancer, benign tumor, or an HPV-related lesion, or reduce the incidence of recurrence thereof, in a patient up to 26 years old (e.g., an infant, a child, an adolescent or a young adult) or, alternatively, an adult patient aged 27 or greater.

[000114] More particularly, one preferred embodiment of the invention comprises a method for the treatment of cancerous or non-cancerous tumor or lesion in a patient comprising the step

of administering to the patient a dose of an HPV recombinant vaccine directly to the lesion, tumor, or non-cancerous HPV-related lesion.

[000115] Alternatively, the method can comprise the following optional steps:

i. administering directly to a cancer lesion, benign tumor, or non-cancerous HPV-related lesion of a patient a second dose of the HPV vaccine between about one month and about three months after the first dose;

ii. administering directly to a cancer lesion, benign tumor, or non-cancerous HPV-related lesion of a patient a subsequent dose of the HPV vaccine between about five months to about seven months after administering the first dose; or

iii. administering directly to a cancer lesion, benign tumor, or non-cancerous HPV-related lesion of a patient a second dose of the HPV vaccine between about one month and about three months after the first dose, and administering directly to a cancer lesion, benign tumor, or non-cancerous HPV-related lesion of a patient a subsequent dose of the HPV vaccine between about five months to about seven months after administering the first dose.

[000116] It would be understood by medical practitioners that the reference to the timing of subsequent administrations of the vaccine is approximate and can vary by days or even weeks. This variation can result from patient compliance or non-compliance to the scheduled dosing, clinical observation by the treating physician who may decide to advance (for more aggressive treatment) or delay a subsequent administration for medical reasons. Generally, however, an effective result can be achieved by following a dosing schedule where the second dose is administered about two months following the first dose, and a third dose at about six months

after the first dose. Additional (fourth, or fifth) doses can be administered if the physician deems that subsequent administrations can provide benefit to the patient.

[000117] Selecting a dosage regimen (also referred to herein as an administration regimen) depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells, tissue or organ in the individual being treated. Preferably, a dosage regimen maximizes the amount of therapeutic agent delivered to the patient consistent with an acceptable level of side effects. Accordingly, the dose amount and dosing frequency depends in part on the particular therapeutic agent, the severity of the cancer being treated, and patient characteristics. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available. See, e.g., Wawrzynczak (1996) Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, NY; Bach (ed.) (1993) Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, NY; Baert et al. (2003) New Engl. J. Med. 348:601-608; Milgrom et al. (1999) New Engl. J. Med. 341 : 1966-1973; Slamon et al. (2001) New Engl. J. Med. 344:783-792; Beniaminovitz et al. (2000) New Engl. J. Med. 342:613-619; Ghosh et al. (2003) New Engl. J. Med. 348:24-32; Lipsky et al. (2000) New Engl. J. Med. 343 : 1594-1602; Physicians' Desk Reference 2003 (Physicians' Desk Reference, 57th Ed); Medical Economics Company; ISBN: 1563634457; 57th edition (November 2002). Determination of the appropriate dosage regimen may be made by the clinician, e.g., using parameters or factors known or suspected in the art to affect treatment or predicted to affect treatment, and will depend, for example, the patient's clinical history (e.g., previous therapy), the type and stage of the cancer to be treated and biomarkers of response to one or more of the therapeutic agents in the combination therapy.

[000118] HPV viral or viral-like proteins of the invention may be administered by continuous infusion, or by doses at intervals of, e.g., daily, every other day, three times per week, or one time each week, two weeks, three weeks, monthly, bimonthly, etc. A total weekly dose is generally at least 0.05 μg/kg, 0.2 μg/kg, 0.5 μg/kg, 1 μg/kg, 10 μg/kg, 100 μg/kg, 0.2 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg body weight or more. See, e.g., Yang et al. (2003) New Engl. J. Med. 349:427-434; Herold et al. (2002) New Engl. J. Med. 346: 1692-1698; Liu et al. (1999) J. Neurol. Neurosurg. Psych. 67:451-456; Portielji et al. (20003) Cancer Immunol. Immunother. 52: 133-144.

[000119] In some embodiments, the dosing regimen will comprise administering the HPV vaccine at a dose of 1, 2, 3, 5 or 10 mg/kg at intervals of about 14 days (± 2 days) or about 21 days (± 2 days) or about 30 days (± 2 days) or about one week (± 2 days), two weeks (± 2 days), three weeks (± 2 days) or four weeks (± 2 days) throughout the course of treatment.

[000120] In other embodiments, the dosing regimen will comprise administering the HPV vaccine at a dose of from about 0.005 mg/kg to about 10 mg/kg, with intra-patient dose escalation. In other escalating dose embodiments, the interval between doses will be progressively shortened, e.g., about 30 days (± 2 days) between the first and second dose, about 14 days (± 2 days) between the second and third doses. In certain embodiments, the dosing interval will be about 14 days (± 2 days), for doses subsequent to the second dose.A typical total dose for each direct or local administration according to the method of the subject invention is about 0.5 ml of the vaccine, e.g., of a commercially available vaccine. Each 0.5 ml dose can be administered, e.g., by intralesional injection, as a bolus of the entire 0.5 ml or can be

administered as a divided dose as a plurality of 0.1-0.2 ml partial administrations into the lesion, an area surrounding the lesion, or both.

[000121] According to certain embodiments, multiple doses of an HPV vaccine may be administered to a subject over a defined time course. The methods include, for example, sequentially administering to a subject multiple doses of an HPV vaccine. As used herein, "sequentially administering" means that each dose of an HPV vaccine is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an HPV vaccine, followed by one or more secondary doses of an HPV vaccine, and optionally followed by one or more tertiary doses of an HPV vaccine.

[000122] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of an HPV vaccine. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of an HPV vaccine (e.g., of the one or more HPV viral or viral-like proteins), but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of an HPV vaccine (e.g., of the one or more HPV viral or viral-like proteins) contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

[000123] In one exemplary embodiment, each secondary and/or tertiary dose is administered 1 to 14 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. In another exemplary embodiment, each secondary and/or tertiary dose is administered 1 to 14 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) months after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of an HPV vaccine which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[000124] These methods may include administering to a patient any number of secondary and/or tertiary doses of an HPV vaccine. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[000125] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 3 months after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 1 to 3 months after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a

patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

[000126] In certain embodiments, the initial dose (e.g., a "loading dose") is higher than either or both of the secondary and tertiary doses. For example, the initial dose can be a loading dose, which is 1.5x, 2x, 2.5x, 3x or more, greater than the secondary dose.

[000127] The above direct or local administration method of treatment can be efficacious for treating skin cancer in the patient, and particularly squamous cell carcinoma, wherein a skin cancer lesion is reduced in size or eliminated following the three administrations of the vaccine.

[000128] The direct or local administration treatment method according to the subject invention can also reduce the incidence of recurrence of cancer, including skin cancer, in the patient.

[000129] The direct or local administration method can also be effective to reduce the size or eliminate a benign tumor, whether or not associated with HPV infection, or an HPV-associated, but non-cancerous, lesion, such as warts, including genital warts, e.g., verruca vulgaris or condyloma accuminata.

[000130] The direct or local administration method can also be effective to reduce the incidence of recurrence of a benign tumor, whether or not associated with HPV infection, or an HPV-associated, but non-cancerous, lesion, such as warts, including genital warts, e.g., verruca vulgaris or condyloma accuminata.

[000131] It is a further unexpected result of the present invention to provide a method of eliminating or reducing the size or incidence of recurrence of skin cancer, and particularly squamous cell carcinoma following direct or local administration of one or more injections of HPV bivalent (types 16 and 18) recombinant vaccine, HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine or an HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine.

[000132] Further unexpected results of the subject direct or local administration method of treatment comprise reducing the size of, eliminating, or reducing the incidence of recurrence of skin lesions that are not associated with HPV infection, such as basal cell carcinoma or melanoma.

[000133] In one embodiment of the subject invention, the direct or local administration method is carried out without the administration of an additional or other immunostimulant or adjuvant.

[000134] In certain embodiments, the subject method can comprise administering an additional or other immunomodulatory agent, e.g., and immunostimulant or adjuvant, with, during or following the administration of the vaccine. Non-limiting examples of immunomodulatory agents useful as part of the subject method include:

1) Vitamin D and its analogues;
2) Sirolimus;
3) Interferon and its analogues;
4) Vitamin A and its analogues, e.g., Soriatane (a retinoid)
5) Imiquimod;
6) Ingenol mebutate; and

7) T4 endonuclease
8) Antimetabolites, e.g. 5 Fluorouracil, Methotrexate
9) cyclooxygenase inhibitors, e.g. Diclofenac

[000135] These agents can be given in combination locally or systemically with, or contemporaneous with, the HPV vaccine as described herein, to enhance the effect of the treatment. For example, in a previously HPV immunized patient having a tumor (skin, lung, or the like), a combination of interferon and HPV antigen vaccine could be given locally. Interferon may or may not also be given at the same time systemically. This administration can enhance local destruction of the tumor or other lesion without the systemic side effects associated with interferon.

[000136] Topical application can be beneficial for several reasons, including the elimination of infection risk caused by injection, but can also be advantageous by wide-spread application over large areas in order to treat precancerous (actinic keratoses) as well as malignant tumors. In addition, the topical administration can provide cosmetic enhancement of the skin, by decreasing that appearance of pigment irregularities, poikiloderma, and scaling.

[000137] It is therefore an object of the subject invention to provide a cost-effective, safe, efficacious, and convenient treatment for reducing or ameliorating the growth or size of a cancer tumor or lesion, including a skin cancer lesion such as SCC, BCC or melanoma tumor or lesion. It is another object of the subject invention to provide a cost-effective, efficacious and convenient treatment for curing skin cancer lesions, and yet another object of the invention to provide a cost-effective, efficacious and convenient method to reduce the incidence of recurrence of cancer, including skin cancer lesions.

[000138] The subject method of treating or reducing the incidence of recurrence of skin cancer comprises administering an HPV vaccine in one or more doses to a patient. In one embodiment, the method includes administration of a first dose of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine to a patient, a second dose of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine approximately two months thereafter, and a third dose of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine approximately four months after the second dose. In a preferred embodiment, each dose is 0.5 ml.

[000139] The subject method can be advantageous in that it can be performed using a commercially available HPV bivalent (types 16 and 18) recombinant vaccine, HPV quadrivalent (types 6, 11, 16, and 18) vaccine or HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine as a therapeutic agent rather than or in addition to its use as a preventive vaccine.

[000140] A preventive vaccine is understood to be a vaccine composition administered prior to exposure to or infection with an agent such as human papilloma virus (HPV). Preventive vaccines for protection against or prevention of HPV infection and associated cancers are commercially available are therefore known to be safe. GARDASIL® is an HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine and GARDASIL® 9, is an HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine currently marketed as a preventive vaccine in the United States by Merck & Co., Inc. Whitehouse Station, NJ 08889 USA. CERVARIX® is an HPV bivalent (types 16 and 18) recombinant vaccine available from GlaxoSmithKline (Brentford, England).

[000141] By use of a commercially available vaccine, the vaccine can be readily accessed by a physician or healthcare practitioner. Moreover, the use of an HPV bivalent (types 16 and 18) recombinant vaccine, an HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine or HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine in accordance with the subject method do not require secondary or additional immunostimulants or adjuvants. These commercially available HPV bivalent (types 16 and 18), HPV quadrivalent (types 6, 11, 16, and 18) or HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccines are free, or substantially free, of host-cell and/or non-L1 viral peptides, polypeptides, or proteins, such as the antigens, E6 or E7.

[000142] Advantageously, the unexpected result of treating cancer, benign tumor, or HPV-related skin lesions, including skin cancers that are associated with HPV infection or skin cancers that are not associated with HPV infection, can be achieved using the subject method as described herein.

[000143] Another embodiment of the subject invention includes a composition for carrying out a method of treatment as described. Compositions comprising the vaccine and an added ingredient – one or more of an active pharmaceutical ingredient, excipient or diluent, for example – are also included as part of the invention. In a composition of the invention, HPV vaccine can be formulated with one or more additional active pharmaceutical ingredients for administration to the patient. Additional active pharmaceutical ingredients can be one or more immunomodulatory agent for modulating the effect of the vaccine, or one or more local anesthetic agent, e.g., lidocaine (with or without epinephrine), for reducing patient discomfort during the injection.

[000144] One embodiment of a composition of the subject invention comprises commercially available HPV vaccine formulated with one or more immunomodulatory agent. The one or more immunomodulatory agent can be selected from the group consisting of:

1) Vitamin D and its analogues;
2) Sirolimus;
3) Interferon and its analogues;
4) Vitamin A and its analogues, e.g., Soriatane (a retinoid)
5) Imiquimod;
6) Ingenol mebutate; and
7) T4 endonuclease
8) Antimetabolites, e.g. 5 Fluorouracil, Methotrexate
9) cyclooxygenase inhibitors, e.g. Diclofenac

[000145] A composition comprising HPV vaccine and at least one immunomodulatory agent can advantageously provide enhanced effect of the anti-cancer therapeutic activity of the HPV vaccine.

[000146] One embodiment of a composition of the subject invention comprises commercially available HPV vaccine formulated with one or more local anesthetic agent. The one or more local anesthetic agent can be selected from the group consisting of: the ester local anesthetics, namely procaine, benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine/larocaine, piperocaine, propoxycaine, procaine, proparacaine, and tetracaine, or the amide local anesthetics, namely, lidocaine, articaine, bupivacaine, cinchocaine, etidocaine, levobupivacaine, lignocaine, mepivacaine, prilocaine, ropivacaine, and trimecaine.

[000147] One example of a composition of the invention comprises a 1:1 (v/v) ratio mixture of 0.5 ml of a commercially available HPV vaccine and 0.5 ml of a commercially

available lidocaine solution (e.g., 0.5% (w/v), 1% (w/v), or 2% (w/v)). The composition can be thoroughly mixed and injected into a patient for treatment. Ratios ranging from 1:10 (v/v) vaccine:anesthetic solution to 10:1 (v/v) vaccine:anesthetic solution can be used, as would be understood in the art.

[000148] The HPV vaccine can also be formulated with one or more excipients or diluents for administration to the patient. Excipients and diluents can include one or more conventional pharmaceutically acceptable ingredients useful for formulating topical preparations, including but not limited to, a base for preparing a cream, emollient, gel, lotion, salve, or the like, and can optionally include penetration enhancers, preservatives, release-controlling agents, solubilizers, stabilizers, thickeners or thinners, or the like.

[000149] Solutions for injection can also include one or more buffer, emollient, diluent, pH adjuster, preservative, solubilizer, stabilizer, or the like.

A topical composition comprising a vaccine useful in accordance with the subject invention can be formulated as is conventionally known in the pharmaceutical arts, and can comprise one or more additional ingredients or excipients, such as an organic or inorganic solvent (aqueous or non-aqueous), stabilizing agent, penetration enhancer, buffer, gelling agent, polymeric agent, lubricant, glidant, cream, wax, suspending agent, surfactant, or the like. The formulation can further include a penetration enhancer, such as DMSO. The formulation can be provided as a topical solution, lotion or shake lotion, ointment, cream, gel, foam, transdermal patch, biofrequency chip, powder, solid, sponge, tape, paste, tincture, micelle or liposome, or the like.

[000150] These compositions can be prepared as a manufactured product which can be shipped, stored, and used as needed, including a later time, or can be compounded at the point of care or remotely for immediate single-use treatment.

[000151] A composition of the invention can include one or more additional active pharmaceutical ingredient without an excipient or diluent, or can include one or more active pharmaceutical ingredient and one or more excipient or diluent.

[000152] A composition of the invention can include one or more excipient or diluent without an additional active pharmaceutical ingredient, or can include one or more excipient or diluent and one or more active pharmaceutical ingredient

EXAMPLES

Example 1 – skin cancer

[000153] The following charts provide the results from the subject method of treatment carried out in three patients experiencing relatively frequent recurrence rates of skin cancer, including squamous cell carcinoma (SCC) as well as basal-cell carcinoma.

[000154] The data presented below represents an average number of distinctive recurrences of skin cancer per month for a period of time prior to and after undergoing the method of treatment described herein.

A. Patient 1

[000155] Patient 1 was administered three 0.5ml doses, including a first 0.5ml dose, a second 0.5ml dose two months later, and a third 0.5ml dose four months after the second dose. In a follow-up exam three months after administration of the third dose of HPV quadrivalent

(types 6, 11, 16, and 18) recombinant vaccine, Patient 1 had experienced zero recurrences of skin cancer, including both SCC and BCC types, during the three-month period. Prior to commencement of the treatment method, Patient 1 had more than 300 distinctive occurrences of skin cancer during his lifetime.

PATIENT 1

	Time Period (Months)	SCC	BCC
Prior to Commencement of Treatment Method	16	1.80	0.25
After Commencement of Treatment Method	16	0.37	0.00

B. Patient 2

[000156] Patient 2 was administered three 0.5ml doses of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine, including a first 0.5 ml dose, a second 0.5ml dose two months later, and a third 0.5ml dose four months after the second dose.

PATIENT 2

	Time Period (Months)	SCC	BCC
Prior to Commencement of Treatment Method	13	2.07	0.53
After Commencement of Treatment Method	13	0.23	0.3

C. Patient 3

[000157] Patient 3 was administered three 0.5ml doses of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine, including a first 0.5ml dose, a second 0.5ml dose two months later, and a third 0.5ml dose eight months after the second dose.

PATIENT 3

	Time Period (Months)	SCC	BCC
Prior to Commencement of Treatment Method	22	0.18	0.13
After Commencement of Treatment Method	22	0.09	0.04

[000158] As a group, each of the patients who underwent the method of treatment using HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine experienced a significant decrease in the number of skin cancer recurrences, as well as improvement in the texture and appearance of the skin with decreased scaling and an increase in general skin suppleness.

[000159] Generally, the method of treatment described herein serves to effectively increase, i.e. boost, the patient's immune surveillance in skin cells in order to decrease the likelihood of a development of abnormal skin cells that produce the skin cancer. The method of the present invention has been shown to treat and prevent recurrence of SCC, and to significantly reduce recurrence of BCC. It is also possible that the increase in immune surveillance, as a result of the treatment method, will concomitantly decrease the incidence of malignant melanoma.

[000160] In one embodiment, the method of treatment for eliminating or reducing the incidence of recurrence of skin cancer includes administering the HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine in the form of an injection directly into the cancerous tissue or an area of tissue immediately surrounding the cancerous tissue.

Example 2 – Breast cancer

[000161] A previously HPV-vaccinated 32-year old woman with no history of breast cancer, no family history, and no risk factors, was diagnosed with metastatic breast cancer. Her main tumor was measured by ultrasound as being about 4.1 centimeters in diameter. These metastatic tumors can double in size in about 12 weeks.

[000162] With the patient's fully informed consent and knowledge, the tumor was directly injected with a standard initial dose (about 0.5 ml) of a commercially available HPV vaccine. A second dose 0.5 ml, diluted with saline and lidocaine to about 3 ml, was directly administered to the tumor about two weeks after the first injection. At that time, it was harder to find the tumor to inject, and was believed to have been reduced in size.

[000163] A follow up ultrasound recently showed that the tumor had been reduced in size to about 2.7 centimeters in diameter, corresponding to an approximate 35% reduction in diameter, and a 75% reduction in tumor volume (volume for a sphere is calculated as 4/3 pi x radius cubed).

[000164] With the expected doubling of size, the tumor should have increased by about 40%. to a tumor diameter of about 4.6 centimeters.

Example 3 – metastatic basosquamous carcinoma

[000165] A 99-year old female presented with metastatic basosquamous carcinoma on the leg. metastatic basosquamous carcinoma, severe enough that she was referred to dermatology for palliative treatment and no further options were available but amputation of the limb to prevent further spreading of the cancer.

[000166] A single injection of a conventional dose (about 0.5 ml) of a commercially available HPV vaccine was administered to the patient, intramuscularly (systemically). Additional standard doses of the HPV vaccine were injected into each of two or more sites of the larger lesions.

[000167] Within four weeks of the treatment with HPV vaccine, the lesions were substantially visually improved, and the cancer had no further spreading on the leg. The patient is currently in remission from further or increased size of the lesions.

Example 4 – penile cancer

A 45 year old HIV-positive man with a two-year history of squamous cell carcinoma of the penis that was recalcitrant to treatment with a variety of topical and surgical methods was treated with three equal doses of GARDASIL®, intramuscularly, in accordance with the label instructions.

Within four days, the patient's pain started to lessen, from a pain scale rating of 9-10 on a 10-scale rating to zero over the course of several weeks.

Recent examinations with confocal microscopy show no evidence of malignancy. Confocal photography can be used to detect cancer on skin without the need for biopsy.

Example 5 – aggressive squamous cell carcinoma

An aggressive rapidly growing recurrent squamous cell carcinoma on the lower extremity of an elderly man with history of renal cell carcinoma, and history of chemotherapy was treated with two intralesional injections of GARDASIL® mixed with lidocaine 1% with epinephrine.

The patient had previously been inoculated with GARDASIL® intramuscularly.

This tumor completely regressed and involuted soon after the first treatment, with no further evidence of malignancy.

Example 6 – prostate cancer

Prostate cancer treatment would involve treating the patient with intramuscular HPV, and can also include direct injection into the prostate.

Example 7 – glioblastoma multiforme

Glioblastoma multiforme treatment would involve treating the patient with intramuscular HPV, and then direct injection into a tumor of glioblasotma multiforme.

Example 8 – cervical cancer

Cervical cancer treatment would involve treating the patient with intramuscular HPV, and can also include direct injection into the cervix.

Example 9 – anal cancer

[000168] Anal cancer treatment would involve treating the patient with intramuscular HPV, and can also include direct injection or topical application to the anus.

[000169] Use of other HPV vaccines in treating cancer or tumors in accordance with the methods described herein, are fully contemplated and are within the scope of the invention.

[000170] While the present invention has been presented in accordance with several preferred and practical embodiments thereof, it is recognized that departures from the instant disclosure are fully contemplated within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A method for treating a patient having skin cancer, benign or cancerous tumor, or a human papilloma virus (HPV)-associated lesion, said method comprising the steps of:

a) administering to the patient, a first dose of an HPV vaccine which is free of host-cell peptide, polypeptide, or protein or a degradant product thereof;

b) administering to the patient a second dose of the HPV vaccine about one month to about three months after the first administration; and

c) optionally, administering to the patient a third dose of the HPV vaccine about five months to about seven months after the first dose.

2. The method of claim 1 wherein the second dose of HPV vaccine is administered about two months after administering the first dose and the optional third dose of HPV vaccine is administered about six months after administering the first dose.

3. The method of claim 1 wherein the HPV vaccine is selected from the group consisting of HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine comprising HPV L1 proteins and HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine comprising HPV L1 proteins.

4. The method of claim 1 wherein the vaccine is substantially free of host-cell early antigen, E6 or E7.

5. The method of claim 1 wherein the method does not comprise or excludes administering to the patient an immunomodulatory agent or adjuvant.

6. The method of claim 1 wherein the skin cancer, benign or cancerous tumor, or HPV-associated lesion is substantially reduced in size or eliminated.

7. The method of claim 1 wherein each dose of HPV vaccine is 0.5 ml.

8. The method of claim 1 wherein the cancer or HPV-associated lesion is selected from the group consisting of squamous cell carcinoma, basal cell carcinoma, melanoma, glandular tumor, adenoma, verruca vulgaris, and condyloma accuminata.

9. The method of claim 1, wherein the patient is 27 years of age or older or is previously not immunized with an HPV vaccine.

10. The method of claim 1 wherein the method further comprises:

establishing a positive diagnosis of skin cancer, diagnosis of benign or cancerous tumor, or diagnosis of HPV infection, prior to administering the first dose of HPV vaccine.

11. The method of claim 1, said method comprising the step of:

a) administering a dose of an HPV vaccine directly to a tumor or skin cancer lesion or an area immediately surrounding the tumor, or skin cancer lesion.

12. The method of claim 1 whereby the incidence of recurrence of the tumor, skin cancer lesion, or HPV-associated lesion is reduced.

13. The method of claim 11 wherein the vaccine is administered by injection.

14. The method of claim 11 wherein the method comprises administering an immunomodulatory agent or adjuvant to the patient.

15. The method of claim 11 wherein the method does not comprise or excludes administering to the patient an immunomodulatory agent or adjuvant.

16. The method of claim 1 wherein the method does not comprise or excludes administering a second composition comprising an immunostimulant or an adjuvant.

17. A pharmaceutical composition comprising:

at least one purified viral L1 protein or fragment thereof;

a second active pharmaceutical ingredient; and

a pharmaceutically-acceptable carrier.

18. The pharmaceutical composition of claim 17, wherein the second active pharmaceutical ingredient is a local anesthetic agent.

19. The pharmaceutical composition of claim 18, wherein the local anesthetic agent is selected from the group consisting of: procaine, benzocaine, chloroprocaine, cocaine, cyclomethycaine, dimethocaine/larocaine, piperocaine, propoxycaine, procaine, proparacaine, and tetracaine, lidocaine, articaine, bupivacaine, cinchocaine, etidocaine, levobupivacaine, lignocaine, mepivacaine, prilocaine, ropivacaine, and trimecaine.

20. The pharmaceutical composition of claim 18, wherein the local anesthetic agent is lidocaine.

21. The pharmaceutical composition of claim 17, wherein the second active pharmaceutical ingredient is an immunomodulatory agent selected from the group consisting of vitamin D, a

vitamin D analogue, vitamin A, a vitamin A analogue, sirolimus, interferon, an interferon analogue, imiquimod, ingenol mebutate, T4 endonuclease, an anti-metabolite and a cyclooxygenase inhibitor.

22. The pharmaceutical composition of claim 21, wherein the anti-metabolite is 5-fluorouracil or methotrexate.

23. The pharmaceutical composition of claim 21, wherein the cyclooxygenase inhibitor is diclofenac.

24. The pharmaceutical composition of claim 17, in an injectable form.

25. The pharmaceutical composition of claim 17, in a topical form.

26. The pharmaceutical composition of claim 17, wherein the at least one purified viral L1 protein or fragment thereof is a human papilloma virus (HPV) L1 protein or fragment thereof.

27. The pharmaceutical composition of claim 26, comprising a purified viral L1 protein or fragment thereof from each of HPV types 6, 11, 16 and 18.

28. The pharmaceutical composition of claim 26, comprising a purified viral L1 protein or fragment thereof from each of HPV types 16, 18, 31, 33, 45, 52 and 58.

29. The pharmaceutical composition of claim 1, wherein the at least one purified viral L1 protein or fragment thereof is present in a virus-like particle (VLP).

30. A method for treating a patient having skin cancer, benign or cancerous tumor, or a human papilloma virus (HPV)-associated lesion, said method comprising the steps of:

a) administering to the patient, a first dose of an HPV vaccine which is free of non-L1 viral peptide, polypeptide, or protein or a degradant product thereof;

b) administering to the patient a second dose of the HPV vaccine about one month to about three months after the first administration; and

c) optionally, administering to the patient a third dose of the HPV vaccine about five months to about seven months after the first dose.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/12; C07K 14/005; C12N 7/00 (2017.01)

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/199.1; 424/204.1; 424/277.1; 514/3.7 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2012/0087937 A1 (COLAU et al) 12 April 2012 (12.04.2012) entire document	1-5, 7, 9-16, 29, 30 ---------- 6, 8, 17-28
Y	US 2014/0323437 A1 (CHEVRON PHILLIPS CHEMICAL) 30 October 2014 (30.10.2014) entire document	6, 8
Y	US 2015/0299197 A1 (ABBVIE INC) 22 October 2015 (22.10.2015) entire document	17-28
A	US 2015/0110824 A1 (GLAXOSMITHKLINE BIOLOGICALS) 23 April 2015 (23.04.2015) entire document	1-30
A	WO 2015/054678 A2 (THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ARKANASAS) 16 April 2015 (16.04.2015) entire document	1-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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(71)申请人 哈普威克斯有限责任公司
地址 美国佛罗里达

(72)发明人 蒂姆·艾恩尼德斯

(74)专利代理机构 北京派特恩知识产权代理有限公司 11270
代理人 陈万青 姚开丽

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(54)发明名称

使用疫苗治疗癌症或皮肤病变的方法和组合物

(57)摘要

提供了一种通过向患者给予一个或多个剂量的HPV重组疫苗来治疗癌症、良性肿瘤或HPV相关病变或降低其复发的发生率的方法，所述癌症、良性肿瘤或HPV相关病变包括皮肤癌，并且特别是鳞状细胞癌(SCC)和基底细胞癌。

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1.一种用于治疗患有皮肤癌、良性肿瘤或癌性肿瘤或人乳头状瘤病毒(HPV)相关病变的患者的方法,所述方法包括以下步骤:

a)向该患者给予第一剂量的、不含宿主细胞肽、多肽或蛋白或其降解产物的HPV疫苗;

b)在第一次给予后约一个月至约三个月,向该患者给予第二剂量的HPV疫苗;以及

c)任选地在该第一剂量后约五个月至约七个月,向该患者给予第三剂量的HPV疫苗。

2.如权利要求1所述的方法,其中在给予该第一剂量后约两个月给予第二剂量的HPV疫苗,并且在给予该第一剂量后约六个月给予任选第三剂量的HPV疫苗。

3.如权利要求1所述的方法,其中该HPV疫苗选自下组,该组由以下组成:包含HPV L1蛋白的HPV四价(6型、11型、16型和18型)重组疫苗和包含HPV L1蛋白的HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗。

4.如权利要求1所述的方法,其中该疫苗基本上不含宿主细胞早期抗原,E6或E7。

5.如权利要求1所述的方法,其中该方法不包括或排除向该患者给予免疫调节剂或佐剂。

6.如权利要求1所述的方法,其中该皮肤癌、良性肿瘤或癌性肿瘤或HPV相关病变的尺寸显著减小或被消除。

7.如权利要求1所述的方法,其中HPV疫苗的每个剂量是0.5ml。

8.如权利要求1所述的方法,其中该癌症或HPV相关病变选自下组,该组由以下组成:鳞状细胞癌、基底细胞癌、黑色素瘤、腺癌、腺瘤、寻常疣和尖锐湿疣。

9.如权利要求1所述的方法,其中该患者是27岁或更大或之前未用HPV疫苗进行免疫。

10.如权利要求1所述的方法,其中该方法进一步包括:

在给予第一剂量的HPV疫苗之前,建立皮肤癌的阳性诊断、良性肿瘤或癌性肿瘤的诊断或HPV感染的诊断。

11.如权利要求1所述的方法,所述方法包括以下步骤:

a)将一剂量的HPV疫苗直接给予至肿瘤或皮肤癌病变或紧邻肿瘤或皮肤癌病变的周围区域。

12.如权利要求1所述的方法,其中肿瘤、皮肤癌病变或HPV相关病变复发的发生率降低。

13.如权利要求11所述的方法,其中该疫苗通过注射给予。

14.如权利要求11所述的方法,其中该方法包括向该患者给予免疫调节剂或佐剂。

15.如权利要求11所述的方法,其中该方法不包括或排除向该患者给予免疫调节剂或佐剂。

16.如权利要求1所述的方法,其中该方法不包括或排除给予包含免疫刺激剂或佐剂的第二组合物。

17.一种药物组合物,其包括:

至少一种纯化的病毒L1蛋白或其片段;

第二活性药物成分;和

药学上可接受的载体。

18.如权利要求17所述的药物组合物,其中该第二活性药物成分是局部麻醉剂。

19.如权利要求18所述的药物组合物,其中该局部麻醉剂选自下组,该组由以下组成:

普鲁卡因、苯佐卡因、氯普鲁卡因、可卡因、环美卡因、二甲卡因/拉罗卡因、哌罗卡因、丙氧卡因、普鲁卡因、丙美卡因、和丁卡因、利多卡因、阿替卡因、布比卡因、辛可卡因、依替卡因、左布比卡因、利多卡因、甲哌卡因、丙胺卡因、罗哌卡因、和三甲卡因。

20.如权利要求18所述的药物组合物，其中该局部麻醉剂是利多卡因。

21.如权利要求17所述的药物组合物，其中该第二活性药物成分是选自下组的免疫调节剂，该组由以下组成：维生素D、维生素D类似物、维生素A、维生素A类似物、西罗莫司、干扰素、干扰素类似物、咪喹莫特、巨大戟醇甲基丁烯酸酯、T4内切核酸酶、抗代谢物和环氧合酶抑制剂。

22.如权利要求21所述的药物组合物，其中该抗代谢物是5-氟尿嘧啶或氨甲蝶呤。

23.如权利要求21所述的药物组合物，其中该环氧合酶抑制剂是双氯芬酸。

24.如权利要求17所述的药物组合物，该药物组合物呈可注射形式。

25.如权利要求17所述的药物组合物，该药物组合物呈局部形式。

26.如权利要求17所述的药物组合物，其中该至少一种纯化的病毒L1蛋白或其片段是人乳头状瘤病毒(HPV)L1蛋白或其片段。

27.如权利要求26所述的药物组合物，其包含来自HPV 6型、11型、16型和18型的每一种的纯化的病毒L1蛋白或其片段。

28.如权利要求26所述的药物组合物，其包含来自HPV 16型、18型、31型、33型、45型、52型和58型中的每一种的纯化的病毒L1蛋白或其片段。

29.如权利要求1所述的药物组合物，其中该至少一种纯化的病毒L1蛋白或其片段存在于病毒样颗粒(VLP)中。

30.一种用于治疗患有皮肤癌、良性肿瘤或癌性肿瘤或人乳头状瘤病毒(HPV)相关病变的患者的方法，所述方法包括以下步骤：

a)向该患者给予第一剂量的、不含非-L1病毒肽、多肽或蛋白或其降解产物的HPV疫苗；

b)在第一次给予后约一个月至约三个月，向该患者给予第二剂量的HPV疫苗；以及

c)任选地，在第一剂量后约五个月至约七个月，向该患者给予第三剂量的HPV疫苗。

使用疫苗治疗癌症或皮肤病变的方法和组合物

技术领域

[0001] 本发明涉及治疗癌症(包括皮肤癌或良性肿瘤或恶性肿瘤),并且更具体地涉及用于治疗癌症或肿瘤或减少其复发的发生率的方法,该方法包括疫苗的给予,包括将包含疫苗的组合物作为治疗剂进行局部给予。

背景技术

[0002] 皮肤癌由三个主要类型组成:即基底细胞癌(BCC)、鳞状细胞癌(SCC)和黑色素瘤,并且是世界上癌症的最常见形式。可理解地,许多年以来不断有研究寻求有效的方法来治疗并且可能治愈这些类型的皮肤癌。

[0003] 普遍接受的是人乳头状瘤病毒(HPV)与造成某些类型的皮肤癌(特别是鳞状细胞癌(SCC))有关。HPV是可以感染人类某些类型的组织的DNA病毒。存在多于三十种HPV亚型,并且这些亚型中的一些与宫颈癌(包括HPV16和HPV18)有关。并不知道HPV是基底细胞癌(BCC)或黑色素瘤的原因或与其有关。

[0004] 已经开发出疫苗并且显示这些疫苗可预防妇女宫颈癌和由HPV感染引起或与其有关的其他病症。GARDASIL®是具有针对HPV(6型、11型、16型和18型)的活性的可商购的疫苗。

[0005] GARDASIL®9是另一种可商购的疫苗,该疫苗被销售用于预防HPV(16型、18型、31型、33型、45型、52型和58型)。GARDASIL®被指定用于年龄为9岁-26岁的女孩和男孩;GARDASIL®9也被指定用于年龄为9岁-26岁的女孩以及用于年龄为9-15岁的男孩。

[0006] 也已经生产了其他疫苗用于治疗HPV的亚型,特别是HPV16和HPV18。被预防性地给予以防止某些HPV感染和相关癌症的GARDASIL®和其他已知的疫苗在本文中被称为“预防性疫苗”。典型地,远离任何特定靶标(例如子宫颈),将这些预防性疫苗皮下或肌内(例如,三角肌)注射进患者中来将其给予用于全身性作用。此外,在暴露于HPV之前普遍接受它们是有效的,并且在暴露于或感染有HPV之后的治疗通常不知道它们是有效的。

[0007] 其他预防性疫苗包括例如,如在中国专利申请号101890160(CN'160)中描述的改进的疫苗组合物,该组合物包括HPV的某些L1蛋白(如在GARDASIL®中)和另外的HPV特异性成分。还建议包含HPV 16型和18型蛋白的预防性疫苗提供对其他HPV类型的交叉保护,如在美国公开号2005/0287161中所描述的。

[0008] 描述了用于治疗的疫苗(本文中被称为“治疗性疫苗”)。然而,这些治疗性疫苗需要比病毒特异性组分更多的成分,例如包含可商购的预防性疫苗(例如GARDASIL®)的HPV L1蛋白。

[0009] 美国公开号2007/0218074描述了包含来自HPV感染细胞的宿主细胞肽的疫苗组合物的用途。存在于感染有HPV的细胞表面上的宿主细胞肽(例如早期抗原E6或E7)是宿主细胞蛋白的片段。用于治疗某些癌症类型的疫苗中的多肽E6或E7的关键性描述于Development of HPV vaccines for HPV-associated head and neck squamous cell

Carcinoma[用于HPV相关的头颈鳞状细胞癌的HPV疫苗的开发],Devaraj等人,Crit Rev Oral Biol Med.[口腔生物学和医学的关键评论]2003;14(5):345-62。另一种包含宿主细胞蛋白(BAX)的疫苗描述于美国专利号8,399,610。

[0010] 包含与HPV-16肽组合的其他或另外的抗原的又另一种疫苗组合物是在美国专利号2011//0070252中描述的疫苗组合物,该疫苗组合物另外需要特洛伊(Trojan)抗原。

[0011] 美国专利号2011/0110979(US '979)和美国专利号2012/0288538(US '538)披露了包含E6或E7多肽(来自感染有HPV的宿主细胞的肽片段)的HPV疫苗的治疗性用途。US '538描述了E6和E7对于诱导转染到HPV感染的细胞中至关重要,并且指出不期望不包含E6或E7的疫苗组合物在不具有E6或E7的细胞(即未感染有HPV的细胞例如BCC)上起作用。在US '979出版物中描述的方法另外需要免疫刺激剂或佐剂。

[0012] 尽管US '979和US '538出版物描述了针对皮肤癌(例如SCC或上皮SCC)的治疗性疫苗的用途,但是它们没有描述针对其他皮肤癌(例如BCC或黑色素瘤)的疫苗的用途,其这可能是基于BCC和黑色素瘤与HPV感染无关的认识。

[0013] 疫苗的上述用途的局限性和缺点可以通过使用根据本发明的方法来克服。在医学和健康领域中需要安全和有效的癌症治疗,包括通常与HPV感染无关的皮肤癌或癌症,其对于患者以及健康从业者是方便的。

发明内容

[0014] 本主题发明涉及用于治疗患有与人乳头状瘤病毒(HPV)感染相关或有关与否的皮肤癌、良性肿瘤或恶性肿瘤或其他皮肤病变的患者的方法,所述方法包括以下步骤:

[0015] 给予患有肿瘤、癌症或其他皮肤病变或需要治疗肿瘤、癌症或其他皮肤病变的患者治疗有效剂量的可商购的HPV疫苗。疫苗可以通过直接施用于(局部)肿瘤或病变,或通过直接注射到肿瘤或病变中而直接给予癌症或病变。可替代地,可以通过全身注射给予疫苗用于治疗用途。根据本主题发明的治疗方法还可包括局部施用、直接或全身注射的任何组合。根据其标签标识,治疗有效剂量可以是常规的、批准的疫苗剂量。

[0016] 在一个实施例中,该方法可以包括:

[0017] a)向年龄为27岁或以上的患者或先前未用HPV疫苗免疫的患者给予第一剂量的、不含宿主细胞肽、多肽或蛋白质或其降解产物的HPV疫苗;

[0018] b)在该第一次给予后约一个月至约三个月,向该患者给予第二剂量的HPV疫苗;并且

[0019] c)任选地在该第一剂量后约五个月至约七个月,向该患者给予第三剂量的HPV疫苗。

[0020] 在根据上述步骤a)的初始常规给予疫苗之后,根据上述步骤b)和c)的第二次或第三次给予可以通过注射,或者可以通过局部给予包含疫苗的组合物。可替代地,步骤b)或c)的第二次或第三次给予可包括注射和通过局部给予。

[0021] 在一个实施例中,在给予该第一剂量后约两个月给予第二剂量的HPV疫苗,并且在给予该第一剂量后约六个月给予第三剂量的HPV疫苗。

[0022] 该HPV疫苗可以选自包含HPV L1蛋白的HPV四价(6型、11型、16型和18型)重组疫苗和包含HPV L1蛋白的HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗,并且优

选是不含或基本上不含宿主细胞早期抗原，例如E6或E7。

[0023] 在一个优选的实施例中，该方法不包括或不给予另外的或其他免疫刺激剂或佐剂。

[0024] 在一个优选的实施例中，该方法包括给予另外的或其他免疫调节剂，例如免疫刺激剂或佐剂。

[0025] 通过实施该方法，可以实质上减小或完全消除癌症或HPV相关病变的尺寸。此外，可以降低癌症或HPV相关病变复发的发生率。该方法可以有效治疗癌症、良性肿瘤或HPV相关病变(如鳞状细胞癌、基底细胞癌、黑色素瘤、寻常疣或尖锐湿疣)或降低其复发的发生率。

[0026] 在一个实施例中，该方法可包含单剂量的疫苗。例如，单剂量的疫苗可以局部给予，或者通过直接注射到肿瘤中或全身注射以减小大小或消除肿瘤。根据医师或保健专业人员需要或确定，医师或保健专业人员可以给予第二剂量或后续剂量。

[0027] 在一个实施例中，需要治疗的患者可以是先前用疫苗免疫的人。在另一个实施例中，需要治疗的患者可以是先前未用疫苗免疫的人。

[0028] 在上述方法步骤中给予的每剂量HPV疫苗优选地为约0.5ml，并且更优选地为0.5ml。

[0029] 该方法可以进一步包括在给予第一剂量的HPV疫苗之前建立癌症、良性肿瘤或HPV感染的阳性诊断。

[0030] 根据本发明的方法的替代性实施例包括治疗患有癌症、良性肿瘤或人乳头状瘤病毒相关的(HPV相关的)病变的患者，其中该方法包括直接向癌症、肿瘤或病变或者紧邻肿瘤或病变的周围区域给予一个剂量的HPV疫苗。

[0031] 根据本发明的方法的该替代性实施例可以进一步包括以下步骤：

[0032] 在给予该第一剂量后约一个月至约三个月，直接向肿瘤或病变或紧邻肿瘤或病变的周围区域给予第二剂量的HPV疫苗；并且

[0033] 任选地，在给予该第一剂量后约五个月至约七个月，直接向肿瘤或病变或紧邻肿瘤或病变的周围区域给予第三剂量的HPV疫苗。

[0034] 包含该疫苗的组合物的这些直接第二次或第三次给予可以是局部施用，或者可以通过注射到病变中。

[0035] 在本方法的该替代性实施例中，可以在给予该第一剂量后约两个月给予第二剂量的HPV疫苗，并且可以在给予该第一剂量后约六个月给予第三剂量的HPV疫苗。

[0036] 通过实施根据本发明的方法的替代性实施例，可以实质上减小或完全消除癌症、肿瘤或HPV相关病变的尺寸。此外，癌症、肿瘤或HPV相关病变复发的发生率可以降低。

[0037] 每一次随后的给予HPV疫苗(如果有的话)的优选剂量是0.5ml。

[0038] 根据本发明的任何实施例的方法可以用于治疗癌症、良性肿瘤或HPV相关的病变，包括但不限于与HPV感染有关或无关的良性肿瘤、鳞状细胞癌、基底细胞癌、黑色素瘤、寻常疣和尖锐湿疣。

[0039] 该方法可以进一步包括在给予第一剂量的HPV疫苗之前建立癌症、良性肿瘤或HPV感染的阳性诊断。

[0040] 在一个优选的实施例中，疫苗的直接或局部给予是通过注射给予，并且更优选地

该方法不包括在给予疫苗同时、期间或之后给予另外的或其他免疫刺激剂或佐剂。

[0041] 可替代地，本主题方法可包括伴随给予疫苗，在给予疫苗期间或之后给予另外的或其他免疫调节剂，例如免疫刺激剂或佐剂。

[0042] 在另一个优选的实施例中，该疫苗可以配制用于局部给予，并以局部溶液或悬浮液的形式例如液体或喷雾、凝胶、乳膏、药膏、软膏剂、泡沫或摩丝诸如此类直接施用于病变。

[0043] 本主题发明可特别地涉及用于治疗肿瘤的方法，其中该方法包括给予患有肿瘤的患者至少一剂量的可商购的HPV疫苗。有利地，已发现本主题方法可有效地用于治疗腺组织例如乳腺、垂体(例如侵入性垂体腺瘤)、前列腺或胰腺中的肿瘤。该实施例可包括将至少一剂量的疫苗直接给予肿瘤本身。

[0044] 本主题发明可以包括全身给予至少一剂量的疫苗，例如通过单独肌内(IM)注射，或与疫苗直接给予肿瘤(同时或不久之前或之后)组合给予。

[0045] 可替代地，在某些情况下，例如，当肿瘤出现在身体表面上或附近时，该方法可以进一步包括单独局部给予至少一剂量的该HPV疫苗，或与直接注射到肿瘤中组合或与全身注射组合，或与直接注射和全身注射组合。

[0046] 包含疫苗的组合物也包括在本发明的一部分中。例如，该HPV疫苗可以与一种或多种另外的活性药物成分一起配制用于给予患者。另外的活性药物成分可以是用于调节该疫苗的效果的一种或多种免疫调节剂，或用于减少注射期间患者的不适的一种或多种局部麻醉剂(例如利多卡因(有或没有肾上腺素))。

[0047] 本发明组合物的一个实例包括0.5ml可商购的HPV疫苗和0.5ml可商购的利多卡因溶液(例如0.5％(w/v)、1％(w/v)或2％(w/v))的1:1(v/v)比例混合物。可以将组合物彻底混合并注射到患者体内进行治疗。如本领域所理解的，可以使用1:10(v/v)疫苗:麻醉剂溶液至10:1(v/v)疫苗:麻醉剂溶液的范围的比例。

[0048] 该HPV疫苗还可以与一种或多种赋形剂或稀释剂一起配制，以给予患者。赋形剂和稀释剂可包括一种或多种用于配制局部制剂的常规药学上可接受的成分，包括但不限于用于制备乳膏、软化剂、凝胶、洗剂、药膏等的基质，并且可任选地包括增渗剂、防腐剂、释放控制剂、增溶剂、稳定剂、增稠剂或稀释剂等。

[0049] 注射用溶液还可包括一种或多种缓冲剂、软化剂、稀释剂、pH调节剂、防腐剂、增溶剂、稳定剂等。

[0050] 这些组合物可以制备成制造的产品，其可以根据需要运输、储存和使用，包括在稍后的时间，或者可以在护理点或远程复合用于立即一次性使用治疗。

[0051] 本发明的组合物可包括一种或多种不含赋形剂或稀释剂的另外的活性药物成分，或可包括一种或多种活性药物成分和一种或多种赋形剂或稀释剂。

[0052] 本发明的组合物可包括一种或多种赋形剂或稀释剂而无需另外的活性药物成分，或可包括一种或多种赋形剂或稀释剂和一种或多种活性药物成分。

[0053] 根据发明人的知识，将仅包含HPV抗原(不含宿主细胞肽)的HPV疫苗给予至先前未免疫的患者或年龄在27岁或以上的成年患者以消除皮肤癌、良性肿瘤或恶性肿瘤或不是HPV相关病变的其他皮肤病变或者降低它们复发的发生率，这在以前还没有被描述过。先前也没有描述过通过局部施用或通过直接注射到病变或肿瘤中直接或局部给予疫苗以消除

病变并降低其复发的发生率。

具体实施方式

[0054] 本发明涉及治疗癌症、良性肿瘤、皮肤癌，例如鳞状细胞癌(SCC)或与人乳头状瘤病毒(HPV)感染相关或不相关的皮肤病变的方法，并且包括治疗源自于腺组织(例如乳腺、垂体、前列腺或胰组织)的肿瘤。根据本主题发明的方法的一个实施例包括给予患有癌症或肿瘤的患者可商购的HPV疫苗，例如HPV四价(6型、11型、16型和18型)重组疫苗。

[0055] 在一个优选的实施例中，本主题方法包括将至少一剂量的HPV疫苗给予先前未用HPV疫苗免疫的患者，或给予27岁或以上的成年患者。出于本发明的目的，先前未用HPV疫苗免疫的患者被称为“未免疫的患者”，不管患者针对其他病症或疾病可能已经接受的其他免疫接种。

[0056] 给药方案可以是通过直接注射、全身注射或局部施用的单次给予，或任何这些给予途径的组合。可替代地，本主题方法可包括通过直接注射、全身注射或局部施用疫苗进行多次(多于一次)给予或多次(相伴的)给予。

[0057] 本主题方法还可包括按照常规接受的疫苗给药系列给予。例如，HPV疫苗典型地使用以下给药方案来进行给予：该方案包含第一剂量，该第一剂量后约两个月的第二剂量、以及该第一剂量后约六个月的第三剂量。这些第二次、第三次或后续给予可以是全身注射，例如常规肌内注射，或者可以通过病灶内注射或通过局部给予直接给予该病变。

[0058] 出人意料地发现本发明的方法实施例在治疗与HPV感染无关的癌症病变或良性肿瘤(例如基底细胞癌(BBC)或黑色素瘤)或者使其发生、复发和/或进展最小化方面具有有益的结果。

[0059] 虽然不限于任何特定的理论，但是提出本发明方法可以增加(即增强)患者的免疫应答，该免疫应答在临床上显示为皮肤细胞中增加的监视，以减少产生皮肤癌(特别是但不限于SCC)的异常皮肤细胞的发育和进展的可能性。

[0060] 可替代地，本发明的方法可以通过其他机制干扰病毒和病毒样蛋白质的固有功能活性。这种干扰将包括由外源和/或环境因素例如紫外线改变或活化的病毒和病毒样物质的完全或部分功能性失活。

[0061] 如本文所用，术语“HPV”和“人乳头状瘤病毒”是指乳头状瘤病毒科的无包膜双链DNA病毒。它们的基因组是圆形的，并且大小约为8千碱基对。大多数HPV编码八种主要蛋白，六种位于“早期”区域(E1-E2)，并且两种位于“晚期”区域(L1(主要衣壳蛋白)和L2(次要衣壳蛋白))。已经鉴定了超过120种HPV类型，并且它们由数字标出(例如，HPV-16、HPV-18等)。

[0062] 在一个实施例中，本主题发明的HPV疫苗包含来自一种、两种、三种、四种、五种、六种、七种、八种、九种、十种或更多种不同HPV类型的一种或多种蛋白(例如，重组L1蛋白)。表达HPV L1蛋白的方法和制备HPV疫苗的方法是本领域已知的，并描述于例如美国专利号5,820,870和6,251,678中，出于所有目的将其全文并入本文作为参考。

[0063] 在一个实施例中，本发明方法中使用的HPV疫苗含有纯化的无活性的病毒或病毒样蛋白，例如可商购的GARDASIL® (其是HPV四价(6型、11型、16型和18型)重组疫苗)，或GARDASIL®9(其是HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗)。在另

一个实施例中，该HPV疫苗是可商购的CERVARIX®，其是HPV二价(16型和18型)的重组疫苗。根据本主题方法的该实施例可用的疫苗优选不含宿主细胞肽和/或非-L1HPV肽、多肽或蛋白(例如早期抗原E6或E7，其为HPV感染细胞的表面上存在的宿主细胞肽的片段)。

[0064] 可以在未免疫的患者中给予该疫苗用于治疗癌性或良性肿瘤，包括与HPV感染无关的癌症病变、与HPV感染有关的癌症(肿瘤或病变)、与HPV感染无关的良性肿瘤、或非癌性HPV相关的病变。

[0065] 可替代地，可以在未免疫患者中给予疫苗以减少癌症、良性肿瘤或HPV相关病变复发的发生率。在另一个实施例中，可以在年龄为27岁或以上的成年患者中给予疫苗以治疗癌症、良性肿瘤或HPV相关病变或降低其复发的发生率。

[0066] 更具体地，本发明的一个优选实施例包括在未免疫的患者或者年龄为27岁或以上的成年患者中治疗癌症、良性肿瘤或HPV相关病变的方法，该方法包括以下步骤：

[0067] i.向该患者给予第一剂量的、不含宿主细胞肽、多肽或蛋白质的HPV重组疫苗；

[0068] ii.在该第一剂量后约一个月和约三个月之间向该患者给予第二剂量的、不含宿主细胞肽、多肽或蛋白质的HPV重组疫苗；并且

[0069] iii.任选地在给予该第一剂量后约五个月至约七个月之间向该患者给予第三剂量的、不含宿主细胞肽、多肽或蛋白质的HPV疫苗。

[0070] 疫苗剂量的第二次或第三次或后续给予可以是全身性的，例如肌内注射，或者可以通过直接给予病变。疫苗组合物直接给予病变可以通过病灶内注射，或者可以局部施用于病变。在另一个实施例中，第二次、第三次或后续给予既是全身性的，并且也可以是通过将疫苗直接施用于病变。对病变的此类的直接给予可以是病灶内注射或通过局部施用配制用于局部给予的疫苗组合物。

[0071] 执业医师应理解的是，随后的疫苗给予的时间的参考是近似的，并且可以变化几天甚至几周。这种变化可以起因于患者对计划的给药的配合或不配合、治疗医师的临床观察，该医师可能由于医疗原因决定提前(用于更积极的治疗)或延迟随后的给予。然而，一般来说，可以通过遵循以下给药方案来实现有效的结果：在该第一剂量后约两个月给予该第二剂量，并且在该第一剂量后约六个月时给予第三剂量。如果医师认为随后的给予可以为该患者提供益处，则可以给予另外的(第四或第五)剂量。

[0072] 根据本主题发明方法的每次给予的典型总剂量是约0.5ml的疫苗，并且优选地是0.5ml的可商购的HPV疫苗。

[0073] 术语“癌症”、“癌性的”或“恶性的”是指或描述哺乳动物中通常以不受调节的细胞生长为特征的生理状况。癌症的实例包括但不限于：心脏类：肉瘤(血管肉瘤、纤维肉瘤、横纹肌肉瘤、脂肪肉瘤)、黏液瘤、横纹肌瘤、纤维瘤、脂肪瘤和畸胎瘤；肺部：支气管肺癌(鳞状细胞癌、未分化小细胞癌、未分化大细胞癌、腺癌)、肺泡(细支气管)癌、支气管腺瘤、肉瘤、淋巴瘤、软骨错构瘤、间皮瘤；胃肠：食管(鳞状细胞癌、腺癌、平滑肌肉瘤、淋巴瘤)、胃(癌、淋巴瘤、平滑肌肉瘤)、胰(管腺癌、胰岛素瘤、高血糖素瘤、胃泌素瘤、类癌肿瘤、舒血管肠肽瘤)、小肠(腺癌、淋巴瘤、类癌肿瘤、卡波西肉瘤、平滑肌瘤、血管瘤、脂肪瘤、神经纤维瘤、纤维瘤)、大肠(腺癌、管状腺瘤、绒毛状腺瘤、错构瘤、平滑肌瘤)结肠直肠；泌尿生殖道：肾(腺癌、肾母细胞瘤(Wilm's tumor)(肾母细胞瘤(nephroblastoma))、淋巴瘤、白血病)、膀胱和尿道(鳞状细胞癌、移行细胞癌、腺癌)、前列腺(腺癌、肉瘤)、睾丸(精原细胞瘤、畸胎瘤、胚

胎癌性细胞、畸胎癌、绒膜癌、肉瘤、间质细胞癌、纤维瘤、纤维腺瘤、腺瘤样瘤、脂肪瘤)；肝：肝癌(肝细胞癌)、胆管癌、肝母细胞癌、血管肉瘤、肝细胞腺瘤、血管瘤；骨：骨原性肉瘤(骨肉瘤)、纤维肉瘤、恶性纤维组织细胞瘤、软骨肉瘤、尤因肉瘤、恶性淋巴瘤(网状细胞肉瘤)、多发骨髓瘤、恶性巨细胞瘤脊索瘤、骨软骨瘤(骨软骨外生骨疣)、良性软骨瘤、软骨母细胞瘤、软骨粘液样纤维瘤、骨样骨瘤和巨细胞瘤；神经系统：头骨(骨瘤、血管瘤、肉芽肿、黄色瘤、畸形性骨炎)、脑脊膜(脑膜瘤、脑膜肉瘤、神经胶质过多)、脑(星形细胞瘤、髓母细胞瘤、胶质瘤、室管膜瘤、生殖细胞瘤(松果体瘤)、多形性胶质母细胞瘤、少突胶质瘤、神经鞘瘤、视网膜母细胞瘤、先天性肿瘤)、脊髓神经纤维瘤、脑膜瘤、胶质瘤、肉瘤)；妇科学的：子宫(子宫内膜癌)、宫颈(宫颈癌、前肿瘤子宫颈非典型增生)、卵巢(卵巢癌[浆液性囊腺癌、粘液性囊腺癌、未分类的癌症]、粒膜细胞肿瘤、塞-莱二氏细胞瘤、无性细胞瘤、恶性畸胎瘤)、阴门(鳞状细胞癌、上皮内癌、腺癌、纤维肉瘤、黑色素瘤)、阴道(透明细胞癌、鳞状细胞癌、葡萄状肉瘤(胚胎性横纹肌肉瘤)、输卵管(癌)、乳房；血液学的：血液(髓细胞性白血病(急性和慢性)、急性淋巴细胞白血病、慢性淋巴细胞白血病、骨髓增生性疾病、多发骨髓瘤、骨髓增生异常综合征)、何杰金氏病、非何杰金氏淋巴瘤(恶性淋巴瘤)；皮肤：恶性黑色素瘤、基底细胞癌、鳞状细胞癌、卡波西肉瘤、发育不良性痣、脂肪瘤、血管瘤、皮肤纤维瘤、瘢痕瘤、银屑病；和肾上腺：成神经细胞瘤。在另一个实施例中，该癌症是癌、淋巴瘤、白血病、母细胞瘤、和肉瘤。此类的癌症的更具体的实例包括鳞状细胞癌、骨髓瘤、小细胞肺癌、非小细胞肺癌、胶质瘤、何杰金氏淋巴瘤、非何杰金氏淋巴瘤、急性髓细胞性白血病(AML)、多发骨髓瘤、胃肠(道)癌、肾癌、卵巢癌、肝癌、淋巴性白血病、淋巴细胞性白血病、结直肠癌、子宫内膜癌、胃癌、前列腺癌、甲状腺癌、黑色素瘤、软骨肉瘤、成神经细胞瘤、胰腺癌、多形性胶质母细胞瘤、宫颈癌、脑癌、胃癌、膀胱癌、肝癌、乳腺癌、结肠癌、和头颈癌。在某些示例性实施例中，癌症是HPV相关癌症。

[0074] 癌症的具体实例包括皮肤癌，例如基底细胞癌和/或鳞状细胞癌以及其他已知的皮肤癌。癌症的另一个实例包括乳腺癌。癌症的又另一个实例包括前列腺癌。又另一个实例包括阴茎癌。癌症的又另一个实例包括卵巢癌、宫颈癌、阴道癌和/或外阴癌。癌症的又另一个实例包括膀胱癌。癌症的又另一个实例包括结直肠癌和/或肛门癌。癌症的又另一个实例包括口咽癌(例如，咽喉癌、软腭癌、舌根癌、腺样癌和/或扁桃体癌)。癌症的又另一个实例包括肾癌。癌症的又另一个实例包括肝癌。

[0075] 在某些示例性实施例中，癌症与Bcl-2相关X蛋白(BAX)和/或Bcl-2同源拮抗剂/杀伤剂(BAK1)的表达降低相关。在其他示例性实施例中，癌症与一种或多种异常线粒体活性相关。在某些示例性实施例中，本发明的HPV疫苗增加肿瘤细胞中的BAX和/或BAK1表达和/或促进肿瘤细胞的凋亡。在其他方面，本发明的维生素D和HPV疫苗的组合增加肿瘤细胞中BAX和/或BAK1的表达和/或促进肿瘤细胞的凋亡。在另一个实施例中，本发明的HPV疫苗调节肿瘤细胞中的一种或多种线粒体活性。

[0076] 根据本主题发明的治疗方法的上述实施例可有效治疗患者的皮肤癌，和特别是鳞状细胞癌，其中皮肤癌病变的尺寸减小或在三次给予疫苗后被消除。

[0077] 根据本发明的治疗方法还可以降低患者中良性肿瘤或癌症肿瘤或病变(包括皮肤癌)复发的发生率。

[0078] 特别地，根据本主题发明的治疗方法包括消除或减小乳腺癌性肿瘤的大小或复发

的发生率，消除或减少前列腺癌性肿瘤中的大小或复发的发生率，消除或减少胰腺癌性肿瘤的大小或复发的发生率，或消除或减少脑垂体癌性肿瘤(例如侵袭性垂体腺瘤)的大小或复发的发生率。

[0079] 可以受益于根据本主题发明的方法使用HPV疫苗治疗的其他具体的类型的癌症或肿瘤包括并且不限于宫颈癌、肛门癌、口咽癌(咽喉癌、软腭癌、舌根癌、或扁桃体癌)、阴道癌、外阴癌、阴茎癌、结直肠癌、膀胱癌、肺癌、肾癌、肝癌、卵巢癌、胰腺粘液性囊性肿瘤、胃窦癌(gastric cancer)或胃癌(stomach cancer)。

[0080] 根据本发明的方法还可以有效地减小HPV有关的但非癌性的病变(例如疣，包括生殖器疣，例如寻常疣或尖锐湿疣)的尺寸或使其消除。

[0081] 本发明另外的意想不到的结果是提供在一次或多次注射HPV四价(6型、11型、16型和18型)重组疫苗后降低皮肤癌(并且特别是鳞状细胞癌)复发的发生率的方法，其中该疫苗基本上不含作为HPV感染细胞的结果存在于感染细胞的表面上的宿主细胞肽、多肽或蛋白质。本发明治疗方法的另外的意想不到的结果包括减小与HPV感染无关的皮肤病变(例如基底细胞癌或黑色素瘤)的尺寸、将其消除或降低其复发的发生率。

[0082] 本发明涉及上述药剂用于癌症的治疗性治疗的用途。因此，将本发明的HPV疫苗组合物并入适于给予的药物组合物中。此类的组合物通常包含HPV病毒或病毒样蛋白和药学上可接受的载体。如在此使用的，语言“药学上可接受的载体”旨在包括与药物给予相容的任何和所有溶剂、分散介质、包衣、抗细菌剂和抗真菌剂、等渗剂以及吸收延迟剂等。这些介质和药剂用于药物活性物质的用途在本领域中是熟知的。除非任何常规介质或试剂与活性化合物不相容，否则考虑在组合物中使用它们。补充的活性化合物也可以并入这些组合物中。

[0083] 配制本发明药物组合物使其与预期的给药途径相容。给予途径的实例包括肠胃外(例如，静脉内(IV)、真皮内、皮下(SC或SQ)、腹膜内的、肌内)、口服(例如，吸入)、经皮(局部)、和经粘膜给予。用于肠胃外、皮内或皮下施用的溶液或悬浮液可以包括以下组分：无菌稀释剂，诸如注射用水、盐水溶液、固定油、聚乙二醇、甘油、丙二醇或其他合成溶剂；抗菌剂，诸如苯甲醇或对羟基苯甲酸甲酯；抗氧化剂，诸如抗坏血酸或亚硫酸氢钠；螯合剂，诸如乙二胺四乙酸；缓冲剂，诸如乙酸盐、柠檬酸盐或磷酸盐，以及用于调节渗透压的试剂，诸如氯化钠或右旋糖。可用酸或碱调节pH，如盐酸或氢氧化钠。肠胃外制剂可以被封装在由玻璃或塑料制成的安瓿、一次性注射器或多剂量小瓶中。

[0084] 适合于可注射使用的药物组合物包括无菌水溶液(在水溶性的情况下)或分散体以及用于临时制备无菌可注射溶液或分散液的无菌粉末。对于静脉内给药，适合的载体包括生理盐水、抑菌水、Cremophor EL™(巴斯夫公司(BASF)，帕西帕尼，新泽西州)或磷酸酯缓冲盐水(PBS)。在所有情况下，该组合物必须是无菌的并且应该具有达到容易注射的程度的流动性。它在制备和存储的条件下必须是稳定的并且必须抗微生物(如细菌和真菌)的污染作用而保存。载体可以是溶剂或分散介质，含有例如水、乙醇、多元醇(例如，甘油、丙二醇和液体聚乙二醇等)、和其合适的混合物。恰当的流动性可例如通过使用包衣如卵磷脂来维持，在分散体的情况下通过维持所需的颗粒大小来维持，或通过使用表面活性剂来维持。防止微生物的作用可以通过不同的抗细菌剂以及抗真菌剂(例如对羟苯甲酸酯、三氯叔丁醇、苯酚、抗坏血酸、硫柳汞等)来实现。在许多情况下，优选在组合物中纳入等渗剂，例如糖、多

元醇(如甘露醇、山梨醇)、氯化钠。可注射组合物的延长吸收可以通过在组合物中包含延迟吸收的试剂(例如,单硬脂酸铝和明胶)来实现。

[0085] 无菌可注射溶液可以通过将所需量的活性化合物根据需要与以上列举的成分中的一种或其组合一起掺入适当溶剂中,随后过滤灭菌来制备。通常,分散液通过将活性化合物掺入无菌媒介物中来制备,该无菌媒介物含有基础分散介质以及来自以上列举的那些成分的所需其他成分。在用于制备无菌可注射溶液的无菌粉末的情况下,优选的制备方法是真空干燥和冷冻干燥,所述方法从其先前的无菌过滤溶液中产生活性成分和任何其他所希望的成分的粉末。

[0086] 口服的组合物通常包括惰性稀释剂或可食用的载体。可将它们封装在明胶胶囊中或压成片剂。用于口服治疗给药的目的,活性化合物可以掺有赋形剂,并以片剂、锭剂或胶囊剂的形式使用。口服组合物也可以使用流体载体制备,以溶液或悬浮液的形式吞咽或摄取,或用作漱口水,其中液体载体中的化合物口服并漱口,并吐出或吞咽。药物相容性的粘合剂和/或佐剂材料可以作为组合物的一部分被包括。片剂、丸剂、胶囊剂、锭剂等可以含有任何以下成分或具有类似性质的化合物:粘合剂,诸如微晶纤维素、黄蓍胶或明胶;赋形剂,诸如,淀粉或乳糖;崩解剂,诸如海藻酸、Primogel或玉米淀粉;润滑剂,诸如硬脂酸镁或Sterotes;助流剂,诸如胶体二氧化硅;甜味剂,诸如蔗糖或糖精;或调味剂,诸如薄荷、水杨酸甲酯或橙香精。

[0087] 为了通过吸入给药,化合物从包含合适的推进剂(例如,气体如二氧化碳,或喷雾剂)的加压容器或分配器以气溶胶喷雾形式来递送。

[0088] 全身性给予还可以通过经粘膜的或经皮的方式进行。对于经粘膜的或经皮的给予而言,可以配制品使用对欲渗透的屏障适当的渗透剂。此类渗透剂通常是本领域中已知的并且包括例如就经粘膜给药而言,洗涤剂、胆盐、以及梭链孢酸衍生物。经粘膜给予可通过使用鼻喷剂或栓剂来完成。对于透皮给药,将活性化合物配制成如本领域通常已知的软膏剂、药膏、凝胶剂或乳膏剂。

[0089] 该化合物也可以制备成栓剂形式(例如,用常规的栓剂基质,例如可可脂和其他甘油酯)或用于直肠递送的保留灌肠剂。

[0090] 在一个实施例中,HPV病毒或病毒样蛋白用载体制备,所述载体将保护化合物免于从体内快速消除,例如控释制剂,包括植入物和微囊化递送系统。可使用生物可降解的、生物相容的聚合物,如乙烯醋酸乙烯酯、聚酸酐、聚乙醇酸、胶原、聚原酸酯及聚乳酸。用于制备此类配制品的方法对本领域的普通技术人员而言应是显而易见的。这些材料也可以从阿尔扎公司(Alza Corporation)和新星制药有限公司(Nova Pharmaceuticals,Inc.)商购获得。脂质体悬浮液(包括以抗病毒抗原的单克隆抗体靶向受感染细胞的脂质体)也可以用作药学上可接受的载体。这些可以根据本领域的普通技术人员已知的方法而制备,例如,如在美国专利号4,522,811中所描述的。

[0091] 特别有利的是以单位剂型配制口服或肠胃外组合物以便给予和剂量均一。如在此使用的单位剂型是指作为针对待治疗受试者的单一剂量适合的物理上离散的单位;每个单位均含有与所需药物载体缔合的、经计算产生所希望的治疗效果的预定量的活性化合物。本发明的单位剂型的规格由如下决定并且直接依赖于:活性化合物的独特特征和待实现的具体治疗效果,和本领域中配制用于治疗个体的这种活性化合物的固有局限性。

[0092] 此类化合物的毒性与治疗效果可以通过在细胞培养物或实验动物中的标准药学程序来确定，例如以确定LD50(50％群体的致死剂量)以及ED50(在50％群体中治疗有效的剂量)。毒性与疗效之间的剂量比为治疗指数，并且它可以被表示为比率LD50/ED50。优选那些表现出大的治疗指数的化合物。尽管可以使用表现出毒副作用的化合物，但应当注意设计一种递送系统，该递送系统将这类化合物靶向到受影响的组织的部位，从而使对未感染的细胞的潜在的损伤降到最小，并且由此减少副作用。

[0093] 从细胞培养测定和动物研究获得的数据可以用于配制一系列的用于在人类中使用的剂量。优选地这类化合物的剂量处于包括ED50在内的循环浓度范围内，有很少的毒性或没有毒性。剂量可以在该范围内变化，这取决于所使用的剂型和使用的给药途径。对于用于本发明方法的任何化合物，均可根据细胞培养试验初步估计治疗有效剂量。在动物模型中可以将剂量配制为达到循环血浆浓度范围，该范围包括如在细胞培养中确定的EC50(即，实现应答的半最大时的测试化合物浓度)。这种信息可以用于更准确地确定人类中有用的剂量。可以例如通过高效液相色谱法来测量血浆中的水平。

[0094] 药物组合物可以同任选的给药说明书一起被包括在容器、包装或分配器中。

[0095] 递送途径可取决于患者的障碍。在某些示例性实施例中，诊断患有皮肤癌的受试者可通过局部给予来给予本发明的HPV疫苗组合物。除了本发明的HPV疫苗组合物之外，可以给予患者第二疗法，例如姑息疗法和/或疾病特异性疗法。第二疗法可以是，例如，症状性的(例如，用于缓解症状)、保护性的(例如，用于减缓或停止疾病进展)、或恢复性的(例如，用于逆转疾病过程)。例如，对于癌症的治疗，症状性的治疗可以进一步包括用作本文进一步描述的组合疗法的另一种化学治疗剂。

[0096] 通常，本发明的HPV疫苗组合物可以通过任何合适的方法给予。如本文所用，局部递送可以指将HPV疫苗组合物直接施用于身体的任何表面，包括眼睛、粘膜、体腔表面或任何内表面。用于局部给予的制剂可以包括透皮贴剂、软膏、洗剂、乳膏、凝胶剂、滴剂、喷雾剂、以及液体。常规的药物载体、水性基质、粉末或油性基质、增稠剂等可以是必要的或希望的。局部给予也可用作选择性地将HPV疫苗组合物递送至受试者的表皮或真皮，或其特定层或下层组织的方法。

[0097] 用于肠胃外给予的配制品可包括无菌水溶液，其也可含有缓冲剂、稀释剂和其他合适的添加剂。心室内注射可以通过例如附着于储存器的心室内导管来促进。对于静脉内使用，应控制溶质的总浓度以使制剂等渗。

[0098] 本发明的HPV疫苗组合物可通过肺部递送给予受试者。肺部递送组合物可以通过吸入分散体来递送，使得分散体内的组合物可以到达肺部，在那里它可以容易地通过肺泡区域直接吸收到血液循环中。肺部递送对于全身递送和对于治疗肺部疾病的局部递送都可以是有效的。

[0099] 肺部递送可以通过不同方法实现，包括使用喷雾、雾化、微粉和干粉基制剂。可以使用液体雾化器、基于气溶胶的吸入器和干粉分散装置来实现递送。计量剂量装置是优选的。使用雾化器或吸入器的一个好处是最小化污染的可能性，因为这些设备是自备的。例如，干粉分散装置递送可以容易地配制成干粉的药物。HPV疫苗组合物可以通过其本身或与合适的粉末载体组合稳定地储存为冻干或喷雾干燥的粉末。用于吸入的组合物的递送可以通过给药定时元件来介导，所述给药定时元件可以包括定时器、剂量计数器、时间测量装置

或时间指示器，当将其结合到所述装置中时在给予气溶胶药物期间能够实现患者的剂量跟踪、顺应性监测和/或剂量触发。

[0100] 可用作载体的药物赋形剂的类型包括稳定剂，例如人血清白蛋白(HSA)、填充剂，例如碳水化合物、氨基酸和多肽；pH调节剂或缓冲剂；盐诸如氯化钠；等等。这些载体可以是结晶或无定形形式，或者可以是两者的混合物。

[0101] 特别有价值的膨胀剂包括相容的碳水化合物、多肽、氨基酸或其组合。合适的碳水化合物包括单糖，如半乳糖、D-甘露糖、山梨糖等；二糖，如乳糖、海藻糖等；环糊精，如2-羟丙基-β-环糊精；和多糖，如棉子糖、麦芽糖糊精、葡聚糖等；醛糖醇，例如甘露醇、木糖醇等。优选的一组碳水化合物包括乳糖、海藻糖、棉子糖麦芽糖糊精和甘露醇。合适的多肽包括阿斯巴甜。氨基酸包括丙氨酸和甘氨酸，其中优选的是甘氨酸。

[0102] 合适的pH调节剂或缓冲剂包括由有机酸和碱制备的有机盐，例如柠檬酸钠、抗坏血酸钠等；柠檬酸钠是优选的。

[0103] 本发明的一种或多种HPV病毒或病毒样蛋白(即HPV疫苗)可通过口服或鼻腔递送给予。例如，通过这些膜给予的药物可以快速起效，提供治疗血浆水平，避免肝脏代谢的首过效应，并避免药物暴露于恶劣的胃肠(GI)环境。另外的优点包括容易进入膜位点，从而可以容易地施用，定位和去除药物。

[0104] 根据本发明的另一个实施例包括通过直接或局部给予(例如注射到皮肤病变处或病变周围的区域)向患者给予HPV疫苗。这种直接给予方法可以用于患有癌症(特别是皮肤癌)的患者。该方法的该实施例还可以用于治疗非癌性(良性)肿瘤或与HPV有关的非癌性病变，例如疣(如寻常疣或尖锐湿疣)。

[0105] 在包括直接注射到病变中或病变周围的实施例中，给药方案可以包括单次给予或多于一次给予。例如，可以遵循如上所述的三次给予给药系列。可替代地，医师可以在直接向病变中或病变周围的初始剂量之后根据需求给予随后的剂量(prn)。对于任何特定的单个时间点的疫苗的分剂量被认为是单次给予。

[0106] 本发明的这种直接给予实施例可以在如下方面具有有益的结果：治疗癌症病变或肿瘤例如基底细胞癌(BBC)或黑色素瘤、或与HPV感染无关的非癌性(良性)肿瘤，或使其发生、复发和/或进展最小化。

[0107] 在本发明的一个实施例中，实施该方法而在本发明的治疗方法同时、期间或之后不给予另外的或其他免疫刺激剂或佐剂。

[0108] 可替代地，本主题方法可包括伴随给予疫苗，在给予疫苗期间或之后给予另外的或其他免疫调节剂，例如免疫刺激剂或佐剂。可用作主题方法一部分的免疫调节剂的非限制性实例包括：

[0109] 1)维生素D及其类似物；

[0110] 2)西罗莫司(Sirolimus)；

[0111] 3)干扰素及其类似物；

[0112] 4)维生素A及其类似物，例如阿维A酸(类视黄醇)

[0113] 5)咪喹莫特；

[0114] 6)巨大戟醇甲基丁烯酸酯；和

[0115] 7)T4内切核酸酶

[0116] 8)抗代谢物,例如5氟尿嘧啶、氨甲蝶呤

[0117] 9)环加氧酶抑制剂,例如双氯芬酸。

[0118] 这些药剂可以与本文所述的HPV疫苗组合局部或全身给予,或与其同时给予,以增强治疗效果。例如,在先前的HPV免疫的具有肿瘤(皮肤、肺或等等)的患者中,可局部给予干扰素和HPV抗原疫苗的组合。干扰素可能或可能不同时全身给予。该给予可以增强肿瘤或其他病变的局部破坏,而没有与干扰素相关的全身副作用。

[0119] 在本发明的另一方面,本发明提供了治疗个体癌症的方法,包括向个体给予组合疗法,所述组合疗法包含HPV疫苗和除HPV疫苗之外的一种或多种另外的化学治疗剂。另外的治疗剂的具体剂量和剂量方案可以进一步改变,并且最佳剂量、给药方案和给药途径将基于所使用的特定治疗剂来确定。

[0120] 化学治疗剂的实例包括烷化剂,例如噻替派和环磷酰胺;烷基磺酸酯,例如白消安、英丙舒凡和泊舒凡;氮杂环丙烷例如苄氧乙亚胺三嗪、卡波醌、meturedopa、和uredopa;亚乙基亚胺和甲基胺类(methylamelamine),包括六甲蜜胺、曲他胺、替派、三亚乙基硫代磷酰胺和三羟甲密胺(trimethylolomelamine);聚乙酸(尤其是布拉他辛和布拉他辛酮);喜树碱(包括合成的类似物拓扑替康);苔藓抑素;卡利他汀(cally statin);CC-1065(包括其阿多来新、卡折来新和比折来新合成类似物);念珠藻环肽(具体地是念珠藻环肽1和念珠藻环肽8);多拉司他汀;多卡米新(包括合成类似物KW-2189和CBI-TMI);艾榴塞洛素;pancrati他汀(pancrati statin);匍枝珊瑚醇;海绵素;氮芥例如苯丁酸氮芥、萘氮芥、胆磷酰胺(cholophosphamide)、雌氮芥、依弗酰胺、氮芥、盐酸甲氧氮芥、美法仑、新氮芥、苯芥胆甾醇、泼尼莫司汀、曲洛磷胺、乌拉莫司汀;亚硝基脲例如卡莫司汀、氯脲菌素、福莫司汀、洛莫司汀、尼莫司汀、雷莫司汀;抗生素例如烯二炔类抗生素(例如,刺孢霉素,尤其是刺孢霉素gammall和刺孢霉素phill,参见例如Agnew,Chem.Intl.Ed.Engl.[应用化学英文国际版],33:183-186(1994);达内霉素,包括达内霉素A;二膦酸盐类,例如氯屈膦酸盐;埃斯波霉素;以及新制癌菌素发色团和相关的色素蛋白烯二炔抗生素发色基)、阿克拉霉素、放线菌素、安曲霉素、重氮丝氨酸、博来霉素、放线菌素、卡拉比星、洋红霉素、嗜癌菌素、色霉素、放线菌素D、柔红霉素、地托比星、6-二氮-5-氧代-L-正亮氨酸、多柔比星(包括吗啉代-多柔比星、氰基吗啉代-多柔比星、2-吡咯啉-多柔比星和去氧多柔比星)、表阿霉素、依索比星、伊达比星醇、马塞罗霉素、丝裂霉素例如丝裂霉素C、霉酚酸、诺拉霉素、橄榄霉素类、培洛霉素、泊非霉素(potfiromycin)、嘌呤霉素、三铁阿霉素、罗多比星、链黑菌素、链脲菌素、杀结核菌素、乌苯美司、净司他丁、佐柔比星;抗代谢药例如氨甲蝶呤和5-氟尿嘧啶(5-FU);叶酸类似物例如二甲叶酸、氨甲蝶呤、蝶罗呤、三甲曲沙;嘌呤类似物例如氟达拉滨、6-巯基嘌呤、硫咪嘌呤、硫鸟嘌呤;嘧啶类似物例如安西他滨、阿扎胞苷、6-氮杂尿苷、卡莫氟、阿糖胞苷、双脱氧尿苷、去氧氟尿苷、依诺他滨、氟尿苷;雄激素类例如卡普睾酮、丙酸屈他雄酮、环硫雄醇、美雄烷、睾内酯;抗-肾上腺例如氨鲁米特、米托坦、曲洛司坦;叶酸补充剂例如亚叶酸(frolinic acid);醋葡醛内酯;醛磷酰胺糖苷;氨基乙酰丙酸;恩尿嘧啶;安吖啶;百垂布西;比生群;依达曲沙;defofamine;地美可辛;地吖醌;依氟鸟氨酸(elformithine);依利醋铵;埃坡霉素;依托格鲁;硝酸镓;羟基脲;香菇多糖;氯尼达明;美登木素生物碱例如美坦辛和安丝菌素;米托胍腙;米托蒽醌;莫哌达醇;二胺硝吖啶;喷司他丁;蛋氨氮芥;吡柔比星;洛索蒽醌;鬼臼酸;2-乙基酰肼;丙卡巴肼;丙亚胺;根霉素;西佐喃;螺锗;细交链孢菌酮酸;

三环乙亚胺醌;2,2',2″-三氯三乙胺;单端孢霉烯类(具体地是T-2毒素、疣孢菌素(verracurin)A、杆孢菌素A和蛇形菌素);乌拉坦;长春地辛;达卡巴嗪;甘露莫司汀;二溴甘露醇;二溴卫矛醇;哌泊溴烷;盖克托辛(gacytosine);阿拉伯糖苷("Ara-C");环磷酰胺;噻替派;紫杉烷,例如紫杉醇和多西他赛;苯丁酸氮芥;吉西他滨;6-硫鸟嘌呤;巯基嘌呤;甲氨蝶呤;铂类似物例如顺铂和卡铂;长春碱;铂;依托泊苷(VP-16);异环磷酰胺;米托蒽醌;长春新碱;长春瑞宾;诺安托;替尼泊苷;依达曲沙;道诺霉素;氨蝶呤;希罗达;伊班膦酸盐;CPT-11;拓扑异构酶抑制剂RFS 2000;二氟甲基鸟氨酸(DMFO);类视黄醇例如视黄酸;卡培他滨;和药学上可接受的盐、酸或以上任一种的衍生物。还包括用于调节或抑制激素对肿瘤的作用的抗激素剂,例如抗雌激素类和选择性雌激素受体调节剂(SERM),包括例如它莫西芬、雷洛昔芬、屈洛昔芬、4-羟基它莫西芬、曲沃昔芬、雷洛西芬(keoxifene)、LY117018、奥那司酮和托瑞米芬(法乐通);抑制酶芳香酶的芳香酶抑制剂,其调节肾上腺中的雌激素产生,例如像,4(5)-咪唑、氨鲁米特、醋酸甲地孕酮、依西美坦、福美坦、法倔唑、伏氯唑、来曲唑和阿那曲唑;和抗雄激素类,如氟他胺、尼鲁米特、比卡鲁胺、亮丙瑞林和戈舍瑞林;和药学上可接受的盐、酸或以上任一种的衍生物。

[0121] 根据标准药物实践,本发明的组合疗法中的每种治疗剂可以单独或在药物(在本文中也称为药物组合物)中给予,所述药物包含治疗剂和一种或多种药学上可接受的载体、赋形剂和稀释剂。

[0122] 本发明的组合疗法中的每种治疗剂可以同时(即,在相同的药物中)、并行(即,以任何顺序一个接一个地给予的单独药物)或以任何顺序依次给予。当组合疗法中的治疗剂处于不同剂型(一种药剂是片剂或胶囊而另一种药剂是无菌液体)和/或以不同的给药方案给予时,例如,至少每天给予的化学治疗剂和较少给予的HPV疫苗,例如每周一次、每两周一次或每三周一次,顺序给予特别有用。

[0123] 在一些实施例中,该HPV疫苗在给予化学治疗剂之前给予,而在其他实施例中,该HPV疫苗在给予化学治疗剂之后给予。在另一个实施例中,该HPV疫苗与化学治疗剂并行给予。

[0124] 在一些实施例中,组合疗法中的至少一种治疗剂使用相同的给药方案(剂量、频率和治疗持续时间)给予,当该治疗剂用作治疗相同癌症的单一疗法时,通常使用该给药方案。在其他实施例中,患者在组合疗法中接受的至少一种治疗剂中的总量低于当该治疗剂用作单一疗法时,例如是较小剂量、较低频率剂量和/或较短治疗持续时间。

[0125] 本发明的组合疗法中的每种治疗剂可以口服或胃肠外给药,包括静脉内、肌肉内、腹膜内、皮下、直肠、局部和经皮的给予途径。

[0126] 可以在手术之前或之后使用本发明的组合疗法来移除肿瘤,并且可以在放射疗法之前,期间或之后使用。

[0127] 在一些实施例中,将本发明的组合疗法给予之前未用生物治疗剂或化学治疗剂治疗的患者,即未治疗的患者。在其他实施例中,将组合疗法给予在用生物治疗剂或化学治疗剂预先治疗后未能实现持续应答的患者,即经历治疗的患者。

[0128] 本发明的组合疗法通常用于治疗肿瘤,该肿瘤足够大以通过触诊、目视观察或通过本领域熟知的成像技术(例如MRI、超声或CAT扫描)发现。

[0129] 任何可商购的HPV疫苗都可以用于直接向癌症或HPV相关病变给予。例如,本发明

方法的该实施例可以包括向病变中或病变周围直接给予包含纯化的无活性的病毒或病毒样蛋白的疫苗，例如可商购的GARDASIL®(其为HPV四价(6型、11型、16型和18型)重组疫苗)或GARDASIL®9(HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗)或CERVARIX®(HPV二价(16型和18型)重组疫苗)。

[0130] 根据本方法的该实施例有用的疫苗可以包括宿主细胞肽、多肽或蛋白质(例如早期抗原E6或E7)，或排除或不含宿主细胞肽、多肽或蛋白质(例如早期抗原E6或E7)。可以给予该疫苗用于在任何年龄的患者(无论是未免疫的患者还是先前用HPV疫苗免疫的患者)中治疗癌症、良性肿瘤或HPV相关病变。

[0131] 疫苗可以直接或局部给予至病变或肿瘤中或其周围，以减少患者中癌症、良性肿瘤或HPV相关病变复发的发生率。

[0132] 在另一个实施例中，可以在至多26岁的患者(例如，婴儿、儿童、青少年或年轻的成年人)中或可替代地在年龄为27岁或更大的成年患者中给予疫苗以治疗癌症、良性肿瘤或HPV相关病变或降低其复发的发生率。

[0133] 更具体地，本发明的一个优选实施例包括用于治疗患者中的癌性或非癌性肿瘤或病变的方法，该方法包括以下步骤：向该患者直接在病变、肿瘤或非癌性HPV相关病变给予HPV重组疫苗的一个剂量。

[0134] 可替代地，该方法可以包括以下可任选的步骤：

[0135] i.在该第一剂量约一个月和约三个月之间直接向患者的癌症病变、良性肿瘤或非癌性HPV相关病变给予第二剂量的HPV疫苗；

[0136] ii.在给予该第一剂量后约五个月至约七个月之间直接向患者的癌症病变、良性肿瘤或非癌性HPV相关病变给予HPV疫苗的随后的剂量；或者

[0137] iii.在第一次给药后约1个月至约3个月之间直接给予患者的癌症病变、良性肿瘤或非癌性HPV相关病变第二剂量的HPV疫苗，并在第一次给药后约5个月至约7个月之间，直接给予患者的癌症病变、良性肿瘤或非癌性HPV相关病变后续剂量的HPV疫苗。

[0138] 执业医师应理解的是，随后的疫苗给予的时间的参考是近似的，并且可以变化几天甚至几周。这种变化可以起因于患者对计划的给药的配合或不配合、治疗医师的临床观察，该医师可能由于医疗原因决定提前(用于更积极的治疗)或延迟随后的给予。然而，一般来说，可以通过遵循以下给药方案来实现有效的结果：在该第一剂量后约两个月给予该第二剂量，并且在该第一剂量后约六个月时给予第三剂量。如果医师认为随后的给予可以为该患者提供益处，则可以给予另外的(第四或第五)剂量。

[0139] 选择给药方案(在本文中也称为给予方案)取决于若干因素，包括实体的血清或组织周转率、症状水平、实体的免疫原性以及被治疗个体的靶细胞、组织或器官的可及性。优选地，给药方案使递送给患者的治疗剂的量最大化，与可接受的副作用水平一致。因此，剂量和给药频率部分取决于特定治疗剂、所治疗癌症的严重程度和患者特征。可以获得选择适当剂量的抗体、细胞因子和小分子的指导。参见例如，Wawrzynczak(1996)Antibody Therapy[抗体疗法]，Bios Scientific Pub.Ltd.[Bios科学出版公司]，英国牛津郡；Kresina(编辑)(1991)Monoclonal Antibodies,Cytokines and Arthritis[单克隆抗体、细胞因子和关节炎]，Marcel Dekker[马塞尔·德克尔出版社]，纽约州纽约市；Bach(编辑)

(1993)Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases[自身免疫性疾病中的单克隆抗体和多肽疗法],Marcel Dekker[马塞尔·德克尔出版社],纽约州纽约市;Baert等人(2003)New Engl.J.Med.[新英格兰医学杂志]348:601-608;Milgrom等人(1999)New Engl.J.Med.[新英格兰医学杂志]341:1966-1973;Slamon等人(2001)New Engl.J.Med.[新英格兰医学杂志]344:783-792;Beniaminovitz等人(2000)New Engl.J.Med.[新英格兰医学杂志]342:613-619;Ghosh等人(2003)New Engl.J.Med.[新英格兰医学杂志]348:24-32;Lipsky等人(2000)New Engl.J.Med.[新英格兰医学杂志]343:1594-1602;Physicians'Desk Reference[医师手册]2003(Physicians'Desk Reference[医师案头参考],第57版);Medical Economics Company[医学经济公司];ISBN:1563634457;第57版(2002年11月)。临床医生可以确定合适的给药方案,例如,使用本领域已知或怀疑影响治疗或预测影响治疗的参数或因素,并且合适的给药方案的确定将取决于例如患者的临床病史(例如,先前的治疗)、待治疗的癌症的类型和阶段以及在组合疗法中对一种或多种治疗剂的应答的生物标志物。

[0140] 本发明的HPV病毒或病毒样蛋白可以通过连续输注给予,或者以每天,每隔一天,每周三次,或每周一次,两周一次,三周一次,每月一次,两月一次的间隔的剂量给予。总的每周一次的剂量通常是至少0.05μg/kg、0.2μg/kg、0.5μg/kg、1μg/kg、10μg/kg、100μg/kg、0.2mg/kg、1.0mg/kg、2.0mg/kg、10mg/kg、25mg/kg、50mg/kg体重或更多。参见,例如Yang等人(2003)New Engl.J.Med.[新英格兰医学杂志]349:427-434;Herold等人(2002)New Engl.J.Med.[新英格兰医学杂志]346:1692-1698;Liu等人(1999)J.Neurol.Neurosurg.Psych.[神经病学神经外科和精神病学杂志]67:451-456;Portielji等人(20003)Cancer Immunol.Immunother.[癌症免疫学免疫疗法]52:133-144。

[0141] 在一些实施例中,给药方案将包括以约1mg/kg、2mg/kg、3mg/kg、5mg/kg或10mg/kg的剂量在整个治疗过程中以间隔为约14天(±2天)或约21天(±2天)或约30天(±2天)或约一周(±2天)、两周(±2天)、三周(±2天)或四周(±2天)给予该HPV疫苗。

[0142] 在其他实施例中,该给药方案将包括以从约0.005mg/kg至约10mg/kg的剂量施用该HPV疫苗,伴随患者体内剂量递增。在其他逐步增加的剂量实施例中,剂量之间的间隔将逐渐缩短,例如,第一和第二次剂量之间约30天(±2天),第二和第三次剂量之间约14天(±2天)。在某些实施例中,对于第二剂量之后的剂量,给药间隔将为约14天(±2天)。根据本主题发明的方法的每个直接或局部给予的典型总剂量为约0.5ml的疫苗,例如可商购的疫苗。每个0.5ml剂量可以例如作为整个0.5ml的推注通过病灶内注射给予,或者可以作为多次0.1ml-0.2ml部分给予的分剂量给予至病变、病变周围的区域、或两者。

[0143] 根据某些实施例,可以在限定的时间过程中向受试者给予多剂量的HPV疫苗。该方法包括,例如,向受试者依次给予多剂量的HPV疫苗。如本文所用,"依次给予"意指HPV疫苗的每个剂量在不同时间点给予受试者,例如,在预定间隔(例如,数小时、数天、数周或数月)隔开的不同日期。本发明包括这样的方法,其包括依次给予患者单一初始剂量的HPV疫苗,然后给予一种或多种第二剂量的HPV疫苗,并且任选地随后给予一种或多种第三剂量的HPV疫苗。

[0144] 术语"初始剂量"、"第二剂量"和"第三剂量"是指HPV疫苗给予的时间顺序。因此,"初始剂量"是在治疗方案开始时给予的剂量(也称为"基线剂量");"第二剂量"是初始剂量

后给予的剂量;“第三剂量”是在第二剂量后给予的剂量。初始剂量、第二剂量和第三剂量可以全部含有相同量的HPV疫苗(例如,一种或多种HPV病毒或病毒样蛋白),但在给予频率方面通常彼此不同。然而,在某些实施例中,在治疗过程中初始剂量、第二剂量和/或第三剂量中含有的HPV疫苗(例如,一种或多种HPV病毒或病毒样蛋白)的量将彼此不同(例如,适当地调高或降低)。

[0145] 在一个示例性实施例中,每个第二剂量和/或第三剂量在其前一剂量后的1至14(例如,1、$1^1/_2$、2、$2^1/_2$、3、$3^1/_2$、4、$4^1/_2$、5、$5^1/_2$、6、$6^1/_2$、7、$7^1/_2$、8、$8^1/_2$、9、$9^1/_2$、10、$10^1/_2$、11、$11^1/_2$、12、$12^1/_2$、13、$13^1/_2$、14、$14^1/_2$或更多)周给予。在另一示例性实施例中,每个第二剂量和/或第三剂量在其前一剂量后的1至14(例如,1、$1^1/_2$、2、$2^1/_2$、3、$3^1/_2$、4、$4^1/_2$、5、$5^1/_2$、6、$6^1/_2$、7、$7^1/_2$、8、$8^1/_2$、9、$9^1/_2$、10、$10^1/_2$、11、$11^1/_2$、12、$12^1/_2$、13、$13^1/_2$、14、$14^1/_2$或更多)周给予。如本文所用,短语“前一剂量”是指以多次给予的顺序中HPV疫苗的剂量,其在顺序中的下一剂量之前给予患者,没有中间剂量。

[0146] 这些方法可包括给予患者任何数量的第二剂量和/或第三剂量的HPV疫苗。例如,在某些实施例中,仅向患者给予单次第二剂量。在其他实施例中,向患者给予两种或更多种(例如,2、3、4、5、6、7、8或更多种)第二剂量。同样地,在某些实施例中,仅向患者给予单次的第三剂量。在其他实施例中,向患者给予两种或更多种(例如,2、3、4、5、6、7、8或更多种)第三剂量。

[0147] 在涉及多个第二剂量的实施例中,每个第二剂量可以与其他第二剂量相同的频率给予。例如,可以在前一剂量后1个月至3个月向患者给予每个第二剂量。类似地,在涉及多个第三剂量的实施例中,每个第三剂量可以与其他第三剂量相同的频率给予。例如,可以在前一剂量后1个月至3个月向患者给予每个第三剂量。可替代地,给予患者第二剂量和/或第三剂量的频率可在治疗方案的过程中变化。给予频率也可以在医师的治疗过程中根据临床检查后个体患者的需要进行调整。

[0148] 在某些实施例中,初始剂量(例如,“负荷剂量”)高于第二剂量和第三剂量中的任一者或两者。例如,初始剂量可以是负荷剂量,其比第二剂量大1.5倍、2倍、2.5倍、3倍或更多倍。

[0149] 上述直接或局部给予治疗方法对于治疗患者中的皮肤癌(特别是鳞状细胞癌)可以是有效的,其中在疫苗的三次给予后,皮肤癌病变在尺寸上减小了或被消除了。

[0150] 根据本发明的直接或局部给予治疗方法还可以降低患者中包括皮肤癌在内的癌症复发的发生率。

[0151] 直接或局部给予方法还可以有效地减小良性肿瘤(无论是否与HPV感染有关)、或HPV有关但非癌性的病变(例如疣,包括生殖器疣,如寻常疣或尖锐湿疣)的尺寸或将其消除。

[0152] 直接或局部给予方法也可以有效地减少良性肿瘤(无论是否与HPV感染有关)、或HPV有关但非癌性的病变(例如疣,包括生殖器疣,例如寻常疣或尖锐湿疣)复发的发生率。

[0153] 本发明的进一步意想不到的结果是提供在一次或多次注射HPV二价(16型和18型)重组疫苗、HPV四价(6型、11型、16型和18型)重组疫苗或HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗的直接或局部给予之后消除皮肤癌(并且特别是鳞状细胞癌)、或减小其尺寸、或降低其复发的发生率的方法。

[0154] 受试者直接或局部给予治疗方法的进一步意想不到的结果包括减小与HPV感染无关的皮肤病变(例如基底细胞癌或黑色素瘤)的尺寸、将其消除或降低其复发的发生率。

[0155] 在本发明的一个实施例中,实施该直接或局部给予方法而不给予另外的或其他免疫刺激剂或佐剂。

[0156] 在某些实施例中,本主题方法可包括伴随给予疫苗,在给予疫苗期间或之后给予另外的或其他免疫调节剂,例如免疫刺激剂或佐剂。可用作主题方法一部分的免疫调节剂的非限制性实例包括:

[0157] 1)维生素D及其类似物;

[0158] 2)西罗莫司(Sirolimus);

[0159] 3)干扰素及其类似物;

[0160] 4)维生素A及其类似物,例如阿维A酸(类视黄醇)

[0161] 5)咪喹莫特;

[0162] 6)巨大戟醇甲基丁烯酸酯;和

[0163] 7)T4内切核酸酶

[0164] 8)抗代谢物,例如5氟尿嘧啶、氨甲蝶呤

[0165] 9)环加氧酶抑制剂,例如双氯芬酸

[0166] 这些药剂可以与本文所述的HPV疫苗组合局部或全身给予,或与其同时给予,以增强治疗效果。例如,在先前的HPV免疫的具有肿瘤(皮肤、肺或等等)的患者中,可局部给予干扰素和HPV抗原疫苗的组合。干扰素可能或可能不同时全身给予。该给予可以增强肿瘤或其他病变的局部破坏,而没有与干扰素相关的全身副作用。

[0167] 局部施用可以是有益的因为几个原因,包括消除由注射引起的感染风险,但是通过广泛使用在大面积上以便治疗癌前(光化性角化病)以及恶性肿瘤也是有利的。此外,局部给予可以通过减少色素不规则、皮肤病和鳞屑的外观来提供皮肤的美容增强。

[0168] 因此,本发明的一个目的是提供成本有效的、安全的、有功效的、和方便的治疗用于减小或减轻癌症肿瘤或病变(包括皮肤癌病变例如SCC)、BCC或黑色素瘤肿瘤或病变的生长或尺寸。本发明的另一个目的是提供成本有效的、有功效的和方便的治疗用于治愈皮肤癌病变,并且本发明的又另一个目的是提供成本有效的、有功效的和方便的方法以减少癌症(包括皮肤癌病变)复发的发生率。

[0169] 治疗皮肤癌或减少其复发的发生率的本发明方法包括以一个或多个剂量向患者给予HPV疫苗。在一个实施例中,该方法包括向患者给予第一剂量的HPV四价(6型、11型、16型和18型)重组疫苗,此后大约两个月给予第二剂量的HPV四价(6型、11型、16型和18型)重组疫苗,以及在该第二剂量后大约四个月给予第三剂量的HPV四价(6型、11型、16型和18型)重组疫苗。在优选的实施例中,每个剂量为0.5ml。

[0170] 本发明方法的优点在于其可以使用可商购的HPV二价(16型和18型)重组疫苗、HPV四价(6型、11型、16型和18型)疫苗或HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗作为治疗剂,而不是或不仅是其作为预防性疫苗的用途来进行。

[0171] 预防性疫苗被理解为在暴露于试剂(例如人乳头状瘤病毒(HPV))或被其感染之前给予的疫苗组合物。因此,可商购的用于保护使免受或预防HPV感染和相关癌症的预防性疫苗已知是安全的。GARDASIL®是HPV四价(6型、11型、16型和18型)重组疫苗,并且

GARDASIL®9是HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗,该重组疫苗目前在美国由美国新泽西州怀特豪斯站(08889)的默克公司(Merck&Co.,Inc.,Whitehouse Station,NJ 08889 USA)作为预防性疫苗销售。CERVARIX®是HPV二价(16和18型)重组疫苗,其购自葛兰素史克公司(GlaxoSmithKline)(英国布伦特福德(Brentford,England))。

[0172] 通过使用可商购的疫苗,该疫苗可以由医师或医疗保健执业医师容易地获得。此外,根据本发明方法使用HPV二价(16型和18型)、HPV四价(6型、11型、16型和18型)重组疫苗或HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗不需要第二或另外的免疫刺激剂或佐剂。这些可商购的HPV二价(16和18型)、HPV四价(6型、11型、16型和18型)或HPV多价(16型、18型、31型、33型、45型、52型和58型)重组疫苗不含或基本上不含宿主细胞和/或非-L1病毒肽、多肽或蛋白(例如抗原E6或E7)。

[0173] 有利地,可以使用如本文所述的本发明方法来实现治疗癌症、良性肿瘤或HPV相关的皮肤病变(包括与HPV感染有关的皮肤癌或与HPV感染无关的皮肤癌)的意想不到的结果。

[0174] 本主题发明的另一个实施例包括用于实施所述治疗方法的组合物。包含疫苗和添加的成分的组合物-例如活性药物成分、赋形剂或稀释剂中的一种或多种-也包括在本发明的一部分中。在本发明的一个组合物中,该HPV疫苗可以与一种或多种另外的活性药物成分一起配制用于给予患者。另外的活性药物成分可以是用于调节该疫苗的效果的一种或多种免疫调节剂,或用于减少注射期间患者的不适的一种或多种局部麻醉剂(例如利多卡因(有或没有肾上腺素))。

[0175] 本主题发明组合物的一个实施例包括用一种或多种免疫调节剂配制的可商购的HPV疫苗。该一种或多种免疫调节剂可选自下组,该组由以下组成:

[0176] 1)维生素D及其类似物;

[0177] 2)西罗莫司(Sirolimus);

[0178] 3)干扰素及其类似物;

[0179] 4)维生素A及其类似物,例如阿维A酸(类视黄醇)

[0180] 5)咪喹莫特;

[0181] 6)巨大戟醇甲基丁烯酸酯;和

[0182] 7)T4内切核酸酶

[0183] 8)抗代谢物,例如5氟尿嘧啶、氨甲蝶呤

[0184] 9)环加氧酶抑制剂,例如双氯芬酸。

[0185] 包含HPV疫苗和至少一种免疫调节剂的组合物可有利地提供HPV疫苗的抗癌治疗活性的增强效果。

[0186] 本主题发明组合物的一个实施例包括用一种或多种局部麻醉剂配制的可商购的HPV疫苗。该一种或多种局部麻醉剂可选自下组,该组由以下组成:酯局部麻醉剂,即普鲁卡因、苯佐卡因、氯普鲁卡因、可卡因、环美卡因、二甲卡因/拉罗卡因、哌罗卡因、丙氧卡因、普鲁卡因、丙美卡因、和丁卡因、或酰胺局部麻醉剂,即,利多卡因、阿替卡因、布比卡因、辛可卡因、依替卡因、左布比卡因、利多卡因、甲哌卡因、丙胺卡因、罗哌卡因、和三甲卡因。

[0187] 本发明组合物的一个实例包括0.5ml可商购的HPV疫苗和0.5ml可商购的利多卡因溶液(例如0.5%(w/v)、1%(w/v)或2%(w/v))的1:1(v/v)比例混合物。可以将组合物彻底

混合并注射到患者体内进行治疗。如本领域所理解的，可以使用1:10(v/v)疫苗:麻醉剂溶液至10:1(v/v)疫苗:麻醉剂溶液的范围的比例。

[0188] 该HPV疫苗还可以与一种或多种赋形剂或稀释剂一起配制，以给予患者。赋形剂和稀释剂可包括一种或多种用于配制局部制剂的常规药学上可接受的成分，包括但不限于用于制备乳膏、软化剂、凝胶、洗剂、药膏等的基质，并且可任选地包括增渗剂、防腐剂、释放控制剂、增溶剂、稳定剂、增稠剂或稀释剂等。

[0189] 注射用溶液还可包括一种或多种缓冲剂、软化剂、稀释剂、pH调节剂、防腐剂、增溶剂、稳定剂等。

[0190] 包含根据本主题发明有用的疫苗的局部组合物可以如制药领域中常规已知的那样配制，并且可以包含一种或多种另外的成分或赋形剂，例如有机或无机溶剂(水性或非水性)、稳定剂、增渗剂、缓冲剂、胶凝剂、聚合物剂、润滑剂、助流剂、乳膏、蜡、悬浮剂、表面活性剂等。该配制品可进一步包括增渗剂，例如DMSO。制剂可以作为局部溶液、洗剂或摇动乳液、软膏、乳膏、凝胶、泡沫、透皮贴剂、生物芯片、粉末、固体、海绵、胶带、糊剂、酊剂、微囊或脂质体等提供。

[0191] 这些组合物可以制备成制造的产品，其可以根据需要运输、储存和使用，包括在稍后的时间，或者可以在护理点或远程复合用于立即一次性使用治疗。

[0192] 本发明的组合物可包括一种或多种不含赋形剂或稀释剂的另外的活性药物成分，或可包括一种或多种活性药物成分和一种或多种赋形剂或稀释剂。

[0193] 本发明的组合物可包括一种或多种赋形剂或稀释剂而无需另外的活性药物成分，或可包括一种或多种赋形剂或稀释剂和一种或多种活性药物成分。

[0194] 实施例

[0195] 实施例1-皮肤癌

[0196] 以下图表提供了来自本发明的治疗方法的结果，该治疗是在经历相对频繁的皮肤癌(包括鳞状细胞癌(SCC)以及基底细胞癌)的复发率的三名患者中实施的。

[0197] 以下呈现的数据表示在经历本文所述的治疗方法之前和之后的一段时间内每月皮肤癌的差别性复发的平均数。

[0198] A.患者1

[0199] 向患者1给予三个0.5ml剂量，该剂量包括第一0.5ml剂量，两个月后的第二0.5ml剂量，以及该第二剂量后四个月的第三0.5ml剂量。在给予第三剂量的HPV四价(6型、11型、16型和18型)重组疫苗后三个月的一项随访检查中，在该三个月的时期中患者1经历了零次皮肤癌(包括SCC和BCC两种类型)的复发。在治疗方法开始之前，患者1在其一生中具有超过300种不同的皮肤癌发生。

[0200] 患者1

[0201]

	时期（月）	SCC	BCC
治疗方法开始之前	16	1.80	0.25
治疗方法开始之后	16	0.37	0.00

[0202] B.患者2

[0203] 向患者2给予HPV四价(6型、11型、16型和18型)重组疫苗的三个0.5ml剂量,该剂量包括第一0.5ml剂量、两个月后的第二0.5ml剂量、以及该第二剂量后四个月的第三0.5ml剂量。

[0204] 患者2

[0205]

	时期	SCC	BCC

[0206]

	(月)		
治疗方法开始之前	13	2.07	0.53
治疗方法开始之后	13	0.23	0.3

[0207] C.患者3

[0208] 向患者3给予HPV四价(6型、11型、16型和18型)重组疫苗的三个0.5ml剂量,该剂量包括第一0.5ml剂量、两个月后的第二0.5ml剂量、以及该第二剂量后八个月的第三0.5ml剂量。

[0209] 患者3

[0210]

	时期 (月)	SCC	BCC
治疗方法开始之前	22	0.18	0.13
治疗方法开始之后	22	0.09	0.04

[0211] 作为一组,经历使用HPV四价(6型、11型、16型和18型)重组疫苗的治疗方法的每位患者都经历了皮肤癌复发数量的显著减少,连同皮肤的纹理和外观的改善(鳞状物减少和普遍皮肤柔软度增加)。

[0212] 通常,本文所述的治疗方法用来有效地增加(即增强)患者在皮肤细胞中的免疫监视,以便于降低产生皮肤癌的异常皮肤细胞的发展的可能性。已经显示本发明的方法治疗和预防SCC复发,并显著降低BCC的复发。作为治疗方法的结果,免疫监视的增加也可能伴随地减少恶性黑色素瘤的发生率。

[0213] 在一个实施例中,用于消除皮肤癌或降低皮肤癌复发的发生率的治疗方法包括将HPV四价(6型、11型、16型和18型)重组疫苗以注射的形式直接给予至癌性组织中或紧邻癌性组织周围的组织区域。

[0214] 实施例2-乳腺癌

[0215] 以前接种过HPV疫苗的32岁妇女,无乳腺癌史,无家族史,并且无危险因素,被诊断患有转移性乳腺癌。通过超声测量她的主要肿瘤直径约4.1厘米。这些转移性肿瘤在大约12周内大小可以加倍。

[0216] 在患者的完全知情同意和了解下,肿瘤直接注射标准初始剂量(约0.5ml)的可商购的HPV疫苗。在第一次注射后约两周,将用盐水和利多卡因稀释至约3ml的第二剂量0.5ml

直接给予肿瘤。那时，发现要注射的肿瘤更难，并且据信其尺寸减小了。

[0217] 最近的随访超声示出，肿瘤的尺寸减小至直径约2.7厘米，相当于直径减少大约35％，并且肿瘤体积减少75％(球体体积计算为4/3)pi x半径立方)。

[0218] 随着预期的大小倍增，肿瘤应该增加约40％至肿瘤直径为约4.6厘米。

[0219] 实施例3-转移性基底鳞状细胞癌

[0220] 一名99岁女性腿部出现转移性基底鳞状细胞癌。转移性基底鳞状细胞癌，严重到足以将她转诊给皮肤科用于姑息治疗，并且没有其他选择，唯有肢体截肢以防止癌症进一步扩散。

[0221] 肌肉内(全身)给予患者单次注射的常规剂量(约0.5ml)的可商购的HPV疫苗。将额外标准剂量的HPV疫苗注射到较大病变的两个或更多个部位的每一个中。

[0222] 在用HPV疫苗治疗的四周内，病变基本上在视觉上得到改善，并且癌症在腿上没有进一步扩散。患者目前从病变的进一步或增大的尺寸中进入缓解期。

[0223] 实施例4-阴茎癌

[0224] 一名患有两年的阴茎鳞状细胞癌(顽抗各种局部和手术方法的治疗)的45岁的HIV阳性的男人用三个相同剂量的GARDASIL®按照标签说明进行肌肉内注射治疗。

[0225] 在四天内，患者的疼痛开始减轻，从10级评定的疼痛评分9-10在几周的过程中降到0。

[0226] 最近的共聚焦显微镜检查示出没有恶性肿瘤的迹象。共聚焦摄影可用于检测皮肤癌，无需活组织检查。

[0227] 实施例5-侵袭性鳞状细胞癌

[0228] 具有肾细胞癌史和化疗史的老人下肢上的侵袭性的快速增长复发性鳞状细胞癌在两个病灶内用GARDASIL®混合1％利多卡因和肾上腺素注射治疗。

[0229] 患者以前曾用GARDASIL®肌肉内注射接种。

[0230] 在第一次治疗后不久，该肿瘤完全消退并消失，没有进一步的恶性肿瘤迹象。

[0231] 实施例6-前列腺癌

[0232] 前列腺癌治疗将涉及用肌肉内HPV治疗患者，并且还可包括直接注射到前列腺中。

[0233] 实施例7-多形性胶质母细胞瘤

[0234] 多形性胶质母细胞瘤治疗包括用肌肉内HPV治疗患者，然后直接注射到多形性胶质母细胞瘤中。

[0235] 实施例8-宫颈癌

[0236] 宫颈癌治疗将涉及用肌肉内HPV治疗患者，并且还可以包括直接注射到子宫颈中。

[0237] 实施例9-肛门癌

[0238] 肛门癌治疗将涉及用肌肉内HPV治疗患者，并且还可包括直接注射或局部施用于肛门。

[0239] 根据本文描述的方法使用其他HPV疫苗治疗癌症或肿瘤是完全预期的并且是在本发明的范围内的。

[0240] 尽管本发明已经根据其若干优选的和实际的实施例呈现了，但是认识到与本披露的偏离情况完全考虑在本发明的精神和范围内。