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(72) Inventor; and
(71) Applicant : **IOANNIDES, Tim** [US/US]; 140 SW Chamber Court, #200, Port St Lucie, FL 34986 (US).

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

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(54) Title: CANCER AND SKIN LESION TREATMENT

(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 (BCC), by administering one or more doses of HPV recombinant vaccine to a patient.

CANCER AND SKIN LESION TREATMENT

BACKGROUND OF THE INVENTION

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

[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] 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 cancer, benign tumor or other skin lesion, has not been previously described. Nor has the direct or local injection of a vaccine to eliminate the lesion and reduce the incidence of its recurrence been previously described.

[00014] 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 skin cancer treatments 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 cancer, benign tumor, or a human papilloma virus-related (HPV-related) lesion, said method comprising the steps of:

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

[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] 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.

[00020] Each dose of HPV vaccine administered in the above method steps is preferably 0.5 ml.

[00021] 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.

[00022] 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.

[00023] 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.

[00024] 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.

[00025] 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 reduced.

[00026] The preferred dose of each administration of HPV vaccine, if any, is 0.5 ml.

[00027] 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.

[00028] 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.

[00029] Preferably, 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.

DETAILED DESCRIPTION

[00030] The present invention is directed to a method of treating cancer, benign tumor, and particularly skin cancer, such as squamous cell carcinoma (SCC), or a skin lesion associated with human papilloma virus (HPV) infection. One embodiment of a method according to the subject invention comprises the administration of an HPV vaccine, such as an HPV quadrivalent (types 6, 11, 16, and 18) recombinant vaccine, to a patient 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.

[00031] The dosing regimen can be 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.

[00032] 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.

[00033] 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.

[00034] 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.

[00035] 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. A vaccine useful in accordance with this embodiment of the subject method is preferably free of host-cell 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.

[00036] 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.

[00037] 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.

[00038] 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. 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.

[00039] 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.

[00040] A typical total dose for each administration according to the method of the subject invention is about 0.5 ml of the vaccine.

[00041] The above 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.

[00042] The treatment method according to the subject invention can also reduce the incidence of recurrence of benign tumors or cancer tumors or lesions, including skin cancer, in the patient.

[00043] The method 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

[00044] 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.

[00045] 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.

[00046] 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.

[00047] 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.

[00048] 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.

[00049] 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,.

[00050] Any effective 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 direct 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.

[00051] 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.

[00052] 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.

[00053] 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 or, alternatively, an adult patient aged 27 or greater.

[00054] 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.

[00055] 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; and

ii. 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 five months to about seven months after administering the first dose.

[00056] 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.

[00057] 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. 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.

[00058] 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.

[00059] 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.

[00060] 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.

[00061] 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

[00062] 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 quadrivalent (types 6, 11, 16, and 18) recombinant vaccine or an HPV multivalent (types 16, 18, 31, 33, 45, 52, and 58) recombinant vaccine.

[00063] 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.

[00064] 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.

[00065] 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.

[00066] 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.

[00067] The subject method can be advantageous in that it can be performed using a commercially available 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.

[00068] 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.

[00069] 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 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 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 peptides, polypeptides, or proteins, such as the antigens, E6 or E7.

[00070] 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.

[00071] 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.

[00072] 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.

Example 1 – Patient 1

[00073] 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

Example 2 – Patient 2

[00074] 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.

19PATIENT 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

Example 3 – Patient 3

[00075] 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

[00076] 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.

[00077] 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.

[00078] 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.

[00079] Use of other HPV vaccines is fully contemplated within the scope of the invention.

[00080] 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 cancer, benign tumor, or a human papilloma virus (HPV)-associated lesion, said method comprising the steps of:

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) 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 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 an additional or other immunostimulant or adjuvant.

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

7. The method of claim 1 wherein the cancer, benign tumor, or HPV-associated lesion is eliminated.

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

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

10. 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, verruca vulgaris, and condyloma accuminata.

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

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

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

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

13. The method of claim 12, further comprising the steps of :

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

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

14. The method of claim 13 wherein 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.

15. The method of claim 12 wherein the cancer, benign tumor, or HPV-associated lesion is eliminated or substantially reduced in size.

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

17. The method of claim 12 wherein the dose of HPV vaccine administered is 0.5 ml.

18. The method of claim 12 wherein the cancer or HPV-associated lesion is selected from the group consisting of squamous cell carcinoma, basal cell carcinoma, melanoma, verruca vulgaris, and condyloma accuminata.

19. The method of claim 12 wherein the method further comprises:

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

20. The method of claim 12 wherein the vaccine is administered by injection.

21. The method of claim 12 wherein the method does not comprise or excludes administering an additional or other immunostimulant or adjuvant.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/57150

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 14/025; A61K 39/00 (2015.01)
CPC - A61K2039/5256; C12N2710/20022; C07K14/005
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)
IPC(8): C07K 14/025; A61K 39/00 (2015.01)
CPC: A61K2039/5256; C12N2710/20022; C07K14/005

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/184.1 (Keyword limited, terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar (NPL)
Keywords: human papilloma virus, HPV vaccine, tumor, lesion, treat, second dose, third dose, E6, E7, age

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	Venugopal et al., 'Recalcitrant Cutaneous Warts Treated With Recombinant Quadrivalent Human Papillomavirus Vaccine (Types 6, 11, 16, and 18) in a Developmentally Delayed, 31-Year-Old White Man,' Arch Dermatol., Vol. 146, No. 5, May 2010 (05.2010) pg. 475-477; pg 475, col 1, para 1-3; pg 476, col 2, para 2.	12-16, 18-21 ---------- 1-11, 17
Y	Villa et al, 'High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up,' British Journal of Cancer, Vol. 95, No. 11, 03 October 2006 (03.10.2006) pg.1459-1466; pg 1460, col 2, para 2; pg 1461, col 1, para 2	1-11, 17
A	US 2010/0189744 A1 (Bryan et al.) 29 July 2010 (29.07.2010) entire document	1-21

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
03 December 2015 (03.12.2015)	29 DEC 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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