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(54) Title: COMPOSITIONS AND METHODS FOR ENHANCING ANTIGEN-SPECIFIC IMMUNE RESPONSES

(57) Abstract: Methods for treating or preventing recurrence of hyper proliferating diseases, e.g., cancer, are described. A method may comprise priming a mammal by administering to the mammal an effective amount of a nucleic acid composition encoding an antigen or a biologically active homo log thereof and boosting the mammal by administering to the mammal an effective amount of an oncolytic virus comprising a nucleic acid encoding the antigen or the biologically active homolog thereof.



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COMPOSITIONS AND METHODS FOR ENHANCING ANTIGEN-SPECIFIC IMMUNE RESPONSES

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 This application claims the benefit of U.S. Provisional Application No. 61/173413, filed on April 28, 2009, the content of which is specifically incorporated by reference herein in its entirety.

GOVERNMENTAL SUPPORT

- 10 This invention was made with government support under grant numbers P50 CA 098252 and RO1 CA 114425, awarded by the U.S. National Cancer Institute. The government has certain rights in this invention.

BACKGROUND

- 15 Cancer immunotherapeutics have shown promise for the treatment of a number of tumors and hyper proliferative diseases, but their utility is limited in situations where the tumor is relatively large or rapidly growing. For example, advanced stage cancers are extremely difficult to treat and rarely result in a cure. Efforts to improve early detection and treatment of advanced stage cancers have been relatively unsuccessful. Existing
20 therapies for advanced disease, such as chemotherapy and radiation therapy, have not improved the overall survival of patients with locally advanced or metastatic disease (Early Breast Cancer Trialists' Collaborative Group, Lancet, 339:1-15 (1992); Baum *et al.*, Salmon SE, ed., Adjuvant therapy of cancer VI. Philadelphia: WB. Saunders, 269-74 (1990); Swain, S.M., Surg. Clin. North Am., 70:1061-80 (1990)). Therefore, there is a strong need
25 to develop innovative therapeutic approaches for the control of hyper proliferative diseases, particularly if they have progressed to an advanced stage.

SUMMARY OF THE INVENTION

- 30 In one embodiment, the invention is directed, at least in part, to a method of inducing or enhancing an antigen-specific immune response in a mammal, comprising the steps of: (a) priming the mammal by administering to the mammal an effective amount of a nucleic acid composition encoding the antigen or a biologically active homolog thereof; and (b) boosting the mammal by administering to the mammal an effective amount of an

oncolytic virus comprising a nucleic acid encoding the antigen or the biologically active homolog thereof, thereby inducing or enhancing the antigen-specific immune response.

In another embodiment, the invention provides a method of inducing or enhancing an antigen-specific immune response in a mammal having a tumor, comprising the steps of:

(a) priming the mammal by administering to the mammal an effective amount of a nucleic acid composition encoding the antigen or a biologically active homolog thereof; and

(b) boosting the mammal by administering to the mammal an effective amount of an oncolytic virus comprising a nucleic acid encoding the antigen or the biologically active homolog thereof, wherein the oncolytic virus is administered intratumorally or peritumorally, thereby inducing or enhancing the antigen-specific immune response.

In some embodiments, the antigen is a tumor-associated antigen (TAA), foreign to the mammal, and/or includes ovalbumin, HPV E6, and HPV E7. In yet another embodiment, the antigen comprises an ovalbumin protein comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:139. In still other embodiments, the antigen comprises an HPV E7 protein comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of LSRHFMHQKRTAMFQDPQERPRKLPQ and AMFQDPQERPRKLPQLCTELQTTIHDIILEC. In one embodiment, the antigen comprises an HPV E7 protein comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of PTLHEYMLDLQPETTDLYCYEQ, HEYMLDLQPET, TLHEYMLDLQPETTD, EYMLDLQPETTDLY, DEIDGPAGQAEPDRAHY and GPAGQAEPDRAHYNI.

In certain embodiments, the nucleic acid composition is a DNA vaccine. In some embodiments, the nucleic acid composition is administered from the group consisting of intradermally, intraperitoneally, and intravenously. In certain embodiments, the mammal is a human having a tumor and wherein the nucleic acid composition is administered intratumorally or peritumorally. In some embodiments,

the oncolytic virus is selected from the group consisting of vaccinia virus, adenovirus, herpes simplex virus, poxvirus, vesicular stomatitis virus, measles virus, Newcastle disease virus, influenza virus, and reovirus. In yet another embodiment, the oncolytic virus is thymidine kinase negative. In certain embodiments, the oncolytic virus is administered from the group consisting of intradermally, intraperitoneally, and intravenously. In some embodiments, the mammal is a human having a tumor and wherein the oncolytic virus is administered intratumorally or peritumorally. In still other embodiments, the nucleic acid composition is present within an oncolytic virus. In other embodiments, the oncolytic virus of step (a) is the same as or is different from the oncolytic virus of step (b). In yet other embodiments, step (a) is performed before step (b), step (a) and step (b) are performed at the same time, or step (a) is performed after step (b). In still another embodiment, step (a) and/or step (b) is repeated at least once. In one embodiment, the dosage used in step (a) and/or step (b) is a range that includes 1×10^7 pfu.

In certain embodiments, the antigen-specific immune response is greater in magnitude than an antigen-specific immune response induced by administration of the nucleic acid composition alone. In other embodiments, the antigen-specific immune response is mediated at least in part by $CD8^+$ cytotoxic T lymphocytes (CTL). In other embodiments, the antigen-specific immune response is mediated at least in part by $CD8^-$ cytotoxic T lymphocytes (CTL) and/or peritumoral stromal cells. In yet another embodiment, the method also includes administering an effective amount of a chemotherapeutic agent.

In still other embodiments, the method includes screening the mammal for the presence of antibodies against the antigen. In some embodiments, the mammal is a human. In other embodiments, the mammal is afflicted with cancer.

The instant invention is also directed at least in part to a method for treating or preventing advanced stage cancer in a mammal comprising (a) priming the mammal by administering to the mammal an effective amount of a nucleic acid composition encoding the antigen or a biologically active homolog thereof; and (b) boosting the mammal by administering to the mammal an effective amount of an oncolytic virus

comprising a nucleic acid encoding the antigen or the biologically active homolog thereof, thereby inducing or enhancing the antigen-specific immune response. In some embodiments, the advanced stage cancer is a cancer described herein, including melanoma or thymoma.

5 The instant invention is also directed at least in part to a kit comprising a priming composition and a boosting composition, the kit comprising; (a) a priming composition comprising DNA encoding an immunogenic foreign antigen and a pharmaceutically acceptable carrier; and (b) a boosting composition comprising a virus encoding said foreign antigen and a pharmaceutically acceptable carrier.

10 The instant invention is also directed to a kit when used in any one of the methods of the invention comprising a priming composition and a boosting composition, the kit comprising:

- (a) a priming composition comprising DNA encoding an immunogenic foreign antigen and a pharmaceutically acceptable carrier; and
- 15 (a) a boosting composition comprising a virus encoding said foreign antigen and a pharmaceutically acceptable carrier.

20 Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

25 Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

BRIEF DESCRIPTION OF THE DRAWINGS

30 **Figures 1A-1B.** Luminescence imaging demonstrating vaccinia infection in mice. Groups of C57BL/6 mice (5 per group) were subcutaneously challenged with 5×10^4 /mouse of TC-1 tumor cells. When tumor size reached about 8-10 mm, mice were treated with either i.t. or i.p. injection of Vac-luc at 1×10^7 pfu/mouse. (A) Representative bioluminescence signal for each group over time.

(B) Bar graph depicting the ratios of signal intensity of intratumoral (i.t.) over intraperitoneal (i.p.) administrations in mice treated with Vac-luc over time.

Figures 2A-2C. *In vivo* tumor treatment experiments with B16 tumors. **(A)** Diagrammatic representation of the prime-boost treatment regimen. Groups of C57BL/6 mice (5 per group) were subcutaneously challenged with 5×10^4 /mouse of B16/F10 tumor cells. 5 days after tumor challenge, mice were immunized with either $2 \mu\text{g}/\text{mouse}$ of pcDNA3 DNA or pcDNA3 expressing ovalbumin (p-OVA) by gene gun. On day 12, mice were boosted by intratumoral injection of 1×10^7 pfu/mouse of either wild-type vaccinia (Vac-WT) or vaccinia encoding ovalbumin (Vac-OVA). B16 tumor-bearing mice treated with 1X PBS were used as a control. **(B)** Line graph depicting the tumor volume in B16 tumor bearing mice treated with the different prime-boost regimens. Numbers in parentheses indicate complete tumor rejection rates. **(C)** Kaplan & Meier survival analysis of B16 tumor bearing mice treated with the different treatment regimens. Data shown are representative of two experiments performed (mean $\pm$ SD).

Figures 3A-3C. *In vivo* tumor treatment experiments with TC-1 tumors. **(A)** Diagrammatic representation of the prime-boost treatment regimen. Groups of C57BL/6 mice (5 per group) were subcutaneously challenged with 5×10^4 /mouse of TC-1 tumor cells. 5 days after tumor challenge, mice were immunized with either $2 \mu\text{g}/\text{mouse}$ of pcDNA3 DNA or pcDNA3 expressing ovalbumin (p-OVA) by gene gun. On day 12, mice were boosted by intratumoral injection of 1×10^7 pfu/mouse of either wild-type vaccinia (Vac-WT) or vaccinia encoding ovalbumin (Vac-OVA). TC-1 tumor-bearing mice treated with 1X PBS were used as a control. **(B)** Line graph depicting the tumor volume in TC-1 tumor bearing mice treated with the different prime-boost regimens. Numbers in parentheses indicate complete tumor rejection rates. **(C)** Kaplan & Meier survival analysis of TC-1 tumor bearing mice treated with the different treatment regimens. Data shown are representative of two experiments performed (mean $\pm$ SD).

Figures 4A-4C. *In vivo* tumor treatment experiments. Groups of C57BL/6 mice (5 per group) were subcutaneously challenged with 5×10^4 /mouse of TC-1 tumor cells. 5 days after tumor challenge, mice were immunized with $2 \mu\text{g}/\text{mouse}$ of pcDNA3 expressing CRT/E7 (p-CRT/E7) by gene gun. On day 12, mice were boosted by intraperitoneal or intratumoral injection of 1×10^7 pfu/mouse of either wild-type vaccinia (Vac-WT) or vaccinia encoding CRT/E7 (Vac-CRT/E7). TC-1 tumor-bearing mice treated with 1X PBS were used as a control. **(A)** Diagrammatic representation of the prime-boost treatment regimen. **(B)** Line graph depicting the tumor volume in TC-1 tumor bearing mice treated with the different prime-boost regimens. Numbers in parentheses indicate complete tumor

rejection rates. **(C)** Kaplan & Meier survival analysis of TC-1 tumor challenged mice treated with the different treatment regimens. * indicates $p < 0.05$. Data shown are representative of two experiments performed (mean+SD).

Figures 5A-5D. Intracellular cytokine staining followed by flow cytometry analysis to determine the number of OVA-specific $CD8^+$ T cells in tumor-bearing mice treated with the different prime-boost regimens. Groups of C57BL/6 mice (5 per group) were challenged subcutaneously with 5×10^4 /mouse of B16/F10 tumor cells. 5 days after tumor challenge, mice were immunized with either pcDNA3 or p-OVA DNA by gene gun and boosted by intratumoral injection of either Vac-WT or Vac-OVA as shown in Figure 2. TC-1 tumor-bearing mice treated with PBS were used as a control. 7 days after vaccinia infection, cells from the spleens (**A & B**) and tumors (**C & D**) of mice were harvested, incubated overnight with the OVA peptide and stained for CD8 and intracellular IFN- γ and then characterized for OVA-specific $CD8^+$ T cells using intracellular IFN- γ staining followed by flow cytometry analysis. **A & C.** Representative flow cytometry data showing the percentage of OVA-specific IFN γ^+ $CD8^+$ T cells in the (A) spleens and (C) tumors of mice treated with the different prime boost regimens. **B & D.** Bar graph depicting the numbers of OVA-specific IFN- γ -secreting $CD8^+$ T cells per 2×10^5 pooled cells in the (**B**) spleens and (**D**) tumors of treated mice. Data shown are representative of two experiments performed (mean $\pm$ SD).

Figures 6A-6B. Intracellular cytokine staining followed by flow cytometry analysis to determine the number of E7-specific $CD8^+$ T cells in tumor-bearing mice treated with the different prime-boost regimens. Groups of C57BL/6 mice (5 per group) were subcutaneously challenged with 5×10^4 /mouse of TC-1 tumor cells. 5 days after tumor challenge, mice were immunized with 2 μ g/mouse of pcDNA3 expressing CRT/E7 (p-CRT/E7) by gene gun. On day 12, mice were boosted by intraperitoneal or intratumoral injection of 1×10^7 pfu/mouse of either wild-type vaccinia (Vac-WT) or vaccinia encoding CRT/E7 (Vac-CRT/E7). TC-1 tumor-bearing mice treated with PBS were used as a control. 7 days after vaccinia infection, cells from the spleens (**A**) and tumors (**B**) of mice were harvested and stained for CD8 and intracellular IFN- γ and then characterized for E7-specific $CD8^+$ T cells using intracellular IFN- γ staining followed by flow cytometry analysis. Bar graph depicting the numbers of OVA-specific IFN- γ -secreting $CD8^+$ T cells per 2×10^5 pooled cells in the (**A**) spleens and (**B**) tumors of treated mice. Data shown are representative of two experiments performed (mean+SD).

Figures 7A-7B. Intracellular cytokine staining followed by flow cytometry analysis to determine the number of OVA-specific CD4⁺ T cells in tumor-bearing mice treated with the different prime-boost regimens. Groups of C57BL/6 mice (5 per group) were challenged subcutaneously with 5x10⁴/mouse of B16/F10 tumor cells. 5 days after tumor challenge, mice were immunized with either pcDNA3 or p-OVA DNA by gene gun and boosted by intratumoral injection of either Vac-WT or Vac-OVA as shown in Figure 2. TC-1 tumor-bearing mice treated with 1X PBS were used as a control. 7 days after vaccinia infection, cells from the spleens (**A**) and tumors (**B**) of mice were harvested and stained for CD8 and intracellular IFN- γ and then characterized for OVA-specific CD4⁺ T cells using intracellular IFN- γ staining followed by flow cytometry analysis. Bar graph depicting the numbers of OVA-specific IFN- γ -secreting CD4⁺ T cells per 2x10⁵ pooled cells in the (**A**) spleens and (**B**) tumors of treated mice. Data shown are representative of two experiments performed (mean $\pm$ SD).

Figures 8A-8B. *In vivo* antibody depletion experiments. C57BL/6 mice (5 per group) were subcutaneously challenged with 5x10⁴/mouse of B16/F10 or TC-1 tumor cells. 5 days after tumor challenge, mice were immunized with 2 μ g/mouse of pcDNA3 expressing ovalbumin (p-OVA) by gene gun. On day 12, mice were boosted by intratumoral injection of 1x10⁷ pfu/mouse of vaccinia encoding ovalbumin (Vac-OVA). Mice were depleted of CD4⁺ or CD8⁺ T cells using antibodies every alternate day starting from D5 for 3 doses followed by once a week until the end of the experiment. Tumor-bearing mice treated with 1X PBS were used as a control. Kaplan & Meier survival analysis of (**A**) B16 or (**B**) TC-1 tumor bearing mice treated with the different treatment regimens.

Figures 9A-9B. *In vitro* cytotoxicity assay. (**A**) Schematic diagram of the experimental design for the cytotoxicity assay. Luciferase-expressing TC-1 tumor cells (2x10⁴/well) were added to 96-well plates. 24 hours later, Vac-WT or Vac-OVA (MOI = 0.5) was added to each well. 48 hours later, the complete medium was changed and activated OT-1 T cells were added to each well at an E:T ratio of 1:1. Bioluminescence imaging was performed 4 hours later. The degree of CTL-mediated killing of the tumor cells was indicated by the decrease of luminescence activity using the IVIS luminescence imaging system series 200. Bioluminescence signals were acquired for 10 seconds. (**B**) Representative luminescence images of 96-well plates and bar graphs depicting the

luminescence intensity in each well containing tumor cells with different treatments (mean $\pm$ SD).

Figures 10A-10B. Characterization of vaccinia infectivity of CD31⁺ cells in tumor. **(A)** Flow cytometry data demonstrating the percentage of CD31⁺ cells in the tumor infected with vaccinia. Groups of C57BL/6 mice (5 per group) were subcutaneously challenged with 5 $\times$ 10⁴/mouse of TC-1 tumor cells. When tumor size reached about 8-10 mm, mice were treated with either intratumorally (i.t.) or intraperitoneally (i.p.) with Vac-GFP at 1 $\times$ 10⁷ pfu/mouse. Tumors were harvested 24 hours after virus injection, stained for CD31 and characterized by flow cytometry analysis. **(B)** Representative bar graphs depicting the number of CD31⁺AAD⁻ cells per 3 $\times$ 10⁵ cells derived from the tumors in the different treatment groups (mean $\pm$ SD). Cells derived from explanted tumors (2 $\times$ 10⁴/well) were added to 96-well plates. 24 hours later, Vac-WT or Vac-OVA (MOI = 0.5) were added to each well and 48 hours later, activated OT-1 T cells (E:T ratio 1:1) were added to each well. 4 hours later, the cells were stained with PE labeled anti-mouse CD31 mAb and FITC labeled 7-AAD and analyzed by flow cytometry analysis.

DETAILED DESCRIPTION

Partial List of Abbreviations

ANOVA, analysis of variance; APC, antigen presenting cell; CRT, calreticulin; CTL, cytotoxic T lymphocyte; DC, dendritic cell; E6, HPV oncoprotein E6; E7, HPV oncoprotein E7; ELISA, enzyme-linked immunosorbent assay; HPV, human papillomavirus; IFN γ , interferon- γ ; i.m., intramuscular(ly); i.t., intratumoral(ly); i.v., intravenous(ly); luc, luciferase; mAB, monoclonal antibody; MOI, multiplicity of infection; OVA, ovalbumin; p-, plasmid-; PBS, phosphate-buffered saline; PCR, polymerase chain reaction; SD, standard deviation; TAA, tumor-associate antigen; Vac, vaccinia virus; WT, wild-type.

Provided herein are methods and compositions for increasing or stimulating an immune response, *e.g.*, for treating and/or preventing recurrence of a hyper proliferating disease, *e.g.*, cancer. In one embodiment, a method comprises priming a mammal by administering to the mammal an effective amount of a composition, including a nucleic acid composition, encoding an antigen or a biologically active homolog thereof and

boosting the mammal by administering to the mammal an effective amount of an oncolytic virus comprising a nucleic acid encoding the antigen or the biologically active homolog thereof. Such methods may be used for therapeutic and/or preventative purposes. Other compositions that may additionally be administered include a protein and/or nucleic acid(s) encoding a protein that enhances the immune system, but do not comprise an antigen, *e.g.*, those that prolong the life of antigen presenting cells, as further described herein.

Other methods may comprise administering a chemotherapeutic agent or drug, *e.g.*, a drug that is not a nucleic acid vaccine, such as a drug that induces apoptosis of cancer cells. Any other combinations of one or more of a nucleic acid encoding an antigen; one or more oncolytic viruses encoding the antigen; one or more immune system enhancing protein(s) and or nucleic acid(s) encoding such a protein; and one or more drugs, *e.g.*, chemotherapeutic drugs, may also be used for stimulating an immune response in a mammal. At least some of the methods may also be used to enhance the efficacy of another treatment, *e.g.*, a treatment that comprises administering an immune system enhancing response in a mammal. Administration of the priming step(s) may be performed at the same time, before or after administration of one or more other agents, *e.g.*, boosting step(s).

Nucleic acid vaccines

Vaccines that may be administered to a mammal include any vaccine, *e.g.*, a nucleic acid vaccine (*e.g.*, a DNA vaccine). In an embodiment of the invention, a nucleic acid vaccine will encode an antigen, *e.g.*, an antigen against which an immune response is desired. Other nucleic acids that may be used are those that increase or enhance an immune reaction, but which do not encode an antigen against which an immune reaction is desired. These vaccines are further described below.

Exemplary antigens include proteins or fragments thereof from a pathogenic organism, *e.g.*, a bacterium or virus or other microorganism, as well as proteins or fragments thereof from a cell, *e.g.*, a cancer cell. In one embodiment, the antigen is from a virus, such as class human papilloma virus (HPV), *e.g.*, E7 or E6. These proteins are also oncogenic proteins, which are important in the induction and maintenance of cellular transformation and co-expressed in most HPV-containing cervical cancers and their precursor lesions. Therefore, cancer vaccines, such as the compositions of the invention, that target E7 or E6 can be used to control of HPV-associated neoplasms (Wu, T-C, *Curr Opin Immunol.* 6:746-54, 1994).

However, as noted, the present invention is not limited to the exemplified antigen(s). Rather, one of skill in the art will appreciate that the same results are expected for any antigen (and epitopes thereof) for which a T cell-mediated response is desired. The response so generated will be effective in providing protective or therapeutic immunity, or both, directed to an organism or disease in which the epitope or antigenic determinant is involved – for example as a cell surface antigen of a pathogenic cell or an envelope or other antigen of a pathogenic virus, or a bacterial antigen, or an antigen expressed as or as part of a pathogenic molecule.

Exemplary antigens and their sequences are set forth below.

E7 Protein from HPV-16

The E7 nucleic acid sequence (SEQ ID NO:8) and amino acid sequence (SEQ ID NO:9) from HPV-16 are shown below (see GenBank Accession No. NC_001526).

15	atg cat gga gat aca cct aca ttg cat gaa tat atg tta gat ttg caa cca gag aca act	60
	Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr Thr	20
	gat ctc tac <u>tgt</u> tat <u>gag</u> caa tta aat gac agc tca gag gag gag gat gaa ata gat ggt	120
	Asp Leu Tyr <u>Cys</u> Tyr <u>Glu</u> Gln Leu Asn Asp Ser Ser Glu Glu Glu Asp Glu Ile Asp Gly	40
	cca gct gga caa gca gaa ccg gac aga gcc cat tac aat att gta acc ttt tgt tgc aag	180
20	Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys	60
	tgt gac tct acg ctt cgg ttg tgc gta caa agc aca cac gta gac att cgt act ttg gaa	240
	Cys Asp Ser Thr Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu	80
	gac ctg tta atg ggc aca cta gga att gtg <u>tgc</u> ccc atc tgt tct cag gat aag ctt	297
	Asp Leu Leu Met Gly Thr Leu Gly Ile Val <u>Cys</u> Pro Ile Cys Ser Gln Asp Lys Leu	99

25 In single letter code, the wild type E7 amino acid sequence (SEQ ID NO:9) is:

MHGDTPTLHE YMLDLQPETT DLYCYEQLND SSEEDEIDG PAGQAEPDRA
HYNIVTFCKK CDSTLRLCVQ STHVDIRTLE DLLMGTLGIV CPICSQDKL 99

In another embodiment (See GenBank Accession No. AF125673, nucleotides 562-858 and the E7 amino acid sequence), the C-terminal four amino acids QDKL (and their codons) above are replaced with the three amino acids QKP (and the codons cag aaa cca), yielding a protein of 98 residues.

When an oncoprotein or an epitope thereof is the immunizing moiety, it is preferable to reduce the tumorigenic risk of the vaccine itself. Because of the potential oncogenicity of the HPV E7 protein, the E7 protein may be used in a “detoxified” form.

35 To reduce oncogenic potential of E7 in a construct of this invention, one or more of the following positions of E7 is mutated:

Original residuc	Mutant residuc	Preferred codon mutation	nt Position (in SEQ ID NO:8)	Amino acid (in SEQ ID NO: 9)
Cys	Gly (or Ala)	TGT→GGT	70	24
Glu	Gly (or Ala)	GAG→GGG (or GCG)	77	26
Cys	Gly (or Ala)	TGC→GGC	271	91

In one embodiment, the E7 (detox) mutant sequence has the following two

mutations:

a TGT→GGT mutation resulting in a Cys→Gly substitution at position 24 of SEQ ID NO:

9 a and GAG→GGG mutation resulting in a Glu→Gly substitution at position 26 of the

5 wild type E7. This mutated amino acid sequence is shown below with the replacement residues underscored:

MHGDPTLHE YMLDLQPETT DLYGYEGLND SSEEDEIDG PAGQAEPDRA
 HYNIVTFCKK CDSTLRCLVQ STHVDIRTLE DLLMGTLGIV CPICSQKP 97 (SEQ
 ID NO: 10)

10 These substitutions completely eliminate the capacity of the E7 to bind to Rb, and thereby nullify its transforming activity. Any nucleotide sequence that encodes the above E7 or E7(detox) polypeptide, or an antigenic fragment or epitope thereof, can be used in the present compositions and methods, including the E7 and E7(detox) sequences are shown above.

15

E6 Protein from HPV-16

The wild type E6 nucleotide (SEQ ID NO:11) and amino acid sequences (SEQ ID NO:12) are shown below (see GenBank accession Nos. K02718 and NC_001526):

	atg cac caa aag aga act gca atg ttt cag gac cca cag gag cga ccc aga aag tta cca	60
20	Met His Gln Lys Arg Thr Ala Met Phe Gln Asp Pro Gln Glu Arg Pro Arg Lys Leu Pro	20
	cag tta tgc aca gag ctg caa aca act ata cat gat ata ata tta gaa tgt gtg tac tgc	120
	Gln Leu Cys Thr Glu Leu Gln Thr Thr Ile His Asp Ile Ile Leu Glu Cys Val Tyr Cys	40
	aag caa cag tta ctg cga cgt gag gta tat gac ttt gct ttt cgg gat tta tgc ata gta	180
	Lys Gln Gln Leu Leu Arg Arg Glu Val Tyr Asp Phe Ala Phe Arg Asp Leu Cys Ile Val	60
25	tat aga gat ggg aat cca tat gct gta tgt gat aaa tgt tta aag ttt tat tct aaa att	240
	Tyr Arg Asp Gly Asn Pro Tyr Ala Val <u>Cys</u> Asp Lys Cys Leu Lys Phe Tyr Ser Lys Ile	80
	agt gag tat aga cat tat tgt tat agt ttg tat gga aca aca tta gaa cag caa tac aac	300
	Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu Tyr Gly Thr Thr Leu Glu Gln Gln Tyr Asn	100
	aaa ccg ttg tgt gat ttg tta att agg tgt att aac tgt caa aag cca ctg tgt cct gaa	360
30	Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys Ile Asn <u>Cys</u> Gln Lys Pro Leu Cys Pro Glu	120
	gaa aag caa aga cat ctg gac aaa aag caa aga ttc cat aat ata agg ggt cgg tgg acc	420
	Glu Lys Gln Arg His Leu Asp Lys Lys Gln Arg Phe His Asn <u>Ile</u> Arg Gly Arg Trp Thr	140
	ggt cga tgt atg tct tgt tgc aga tca tca aga aca cgt aga gaa acc cag ctg <i>taa</i>	474

Gly Arg Cys Met Ser Cys Cys Arg Ser Ser Arg Thr Arg Arg Glu Thr Gln Leu stop 158

This polypeptide has 158 amino acids and is shown below in single letter code (SEQ ID NO:12):

5 MHQKRTAMFQ DPQERPRKLP QLCTELQTTI HDIILECVYC KQQLLRREVY
DFAFRDLCIV YRDGNPYAVC DKCLKFYSKI SEYRHYCYSL YGTTLEQQYN
KPLCDLLIRC INCQKPLCPE EKQRHLDKKQ RFHNIRGRWT GRCMSCCRSS
RTRRETQL 158

E6 proteins from cervical cancer-associated HPV types such as HPV-16 induce
10 proteolysis of the p53 tumor suppressor protein through interaction with E6-AP. Human
mammary epithelial cells (MECs) immortalized by E6 display low levels of p53. HPV-16
E6, as well as other cancer-related papillomavirus E6 proteins, also binds the cellular
protein E6BP (ERC-55). As with E7, described below a non-oncogenic mutated form of E6
may be used, referred to as "E6(detox)." Several different E6 mutations and publications
15 describing them are discussed below.

The amino acid residues to be mutated are underscored in the E6 amino acid
sequence above. Some studies of E6 mutants are based upon a shorter E6 protein of 151
nucleic acids, wherein the N-terminal residue was considered to be the Met at position 8 in
the wild type E6. That shorter version of E6 is shown below as (SEQ ID NO:13):

20 MFQDPQERPR KLPQLCTELQ TTIHDIILEC VYCKQQLLRR EVYDFAFRDL
CIVYRDGNPY AVCDKCLKFY SKISEYRHYC YSLYGTTLEQ QYNKPLCDLL
IRCINCQKPL CPEEKQRHLD KKQRFHNIRG RWTGRCMSCC RSSRTRRETQ L

To reduce oncogenic potential of E6 in a construct, one or more of the following
positions of E6 is mutated:

Original residue	Mutant residue	aa position in SEQ ID NO: 12	aa position in SEQ ID NO: 13
Cys	Gly (or Ala)	70	63
Cys	Gly (or Ala)	113	106
Ile	Thr	135	128

25 Nguyen *et al.*, *J Virol.* 6:13039-48, 2002, described a mutant of HPV-16 E6
deficient in binding α -helix partners which displays reduced oncogenic potential *in vivo*.
This mutant, which includes a replacement of Ile with Thr as position 128 (of SEQ ID NO:
13), may be used in accordance with the present invention to make an E6 DNA vaccine
30 that has a lower risk of being oncogenic. This E6(I¹²⁸T) mutant is defective in its ability to

bind at least a subset of α -helix partners, including E6AP, the ubiquitin ligase that mediates E6-dependent degradation of the p53 protein.

Cassetti MC *et al.*, *Vaccine* 22:520-52, 2004, examined the effects of mutations four or five amino acid positions in E6 and E7 to inactivate their oncogenic potential. The following mutations were examined: E6-C⁶³G and E6 C¹⁰⁶G (positions based on the wild type E6); E7-C²⁴G, E7-E²⁶G, and E7 C⁹¹G (positions based on the wild type E7). Venezuelan equine encephalitis virus replicon particle (VRP) vaccines encoding mutant or wild type E6 and E7 proteins elicited comparable CTL responses and generated comparable antitumor responses in several HPV16 E6(+)E7(+) tumor challenge models: protection from either C3 or TC-1 tumor challenge was observed in 100% of vaccinated mice. Eradication of C3 tumors was observed in approximately 90% of the mice. The predicted inactivation of E6 and E7 oncogenic potential was confirmed by demonstrating normal levels of both p53 and Rb proteins in human mammary epithelial cells infected with VRPs expressing mutant E6 and E7 genes.

The HPV16 E6 protein contains two zinc fingers important for structure and function; one cysteine (C) amino acid position in each pair of C-X-X-C (where X is any amino acid) zinc finger motifs may be mutated at E6 positions 63 and 106 (based on the wild type E6). Mutants are created, for example, using the Quick Change Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA). HPV16 E6 containing a single point mutation in the codon for Cys¹⁰⁶ in the wild type E6 (= Cys 113 in the wild type E6). Cys¹⁰⁶ neither binds nor facilitates degradation of p53 and is incapable of immortalizing human mammary epithelial cells (MEC), a phenotype dependent upon p53 degradation. A single amino acid substitution at position Cys⁶³ of the wild type E6 (=Cys⁷⁰ in the wild type E6) destroys several HPV16 E6 functions: p53 degradation, E6TP-1 degradation, activation of telomerase, and, consequently, immortalization of primary epithelial cells.

Any nucleotide sequence that encodes these E6 polypeptides, one of the mutants thereof, or an antigenic fragment or epitope thereof, can be used in the present invention. Other mutations can be tested and used in accordance with the methods described herein including those described in Cassetti *et al.*, *supra*. These mutations can be produced from any appropriate starting sequences by mutation of the coding DNA.

The present invention also includes the use of a tandem E6-E7 vaccine, using one or more of the mutations described herein to render the oncoproteins inactive with respect to their oncogenic potential *in vivo*. VRP vaccines (described in Cassetti *et al.*, *supra*)

comprised fused E6 and E7 genes in one open reading frame which were mutated at four or five amino acid positions. Thus, the present constructs may include one or more epitopes of E6 and E7, which may be arranged in their native order or shuffled in any way that permits the expressed protein to bear the E6 and E7 antigenic epitopes in an immunogenic form. DNA encoding amino acid spacers between E6 and E7 or between individual epitopes of these proteins may be introduced into the vector, provided again, that the spacers permit the expression or presentation of the epitopes in an immunogenic manner after they have been expressed by transduced host cells.

10 *Ovalbumin (OVA)*

An amino acid sequences encoding a representative OVA (SEQ ID NO:139) is shown below.

MGSIGAASMEFCFDVFKELKVHHANENIFYCPIAIMSALAMVYLGAKDSTRQINK
 VVRFDKLPGFSGDSIEAQCGTSVNV
 15 HSSLRDILNQITKPNDVYSFSLASRLYAEERYPILPEYLQCVKELYRGGLEPINFQTA
 ADQARELINSWVESQTNGIIRN
 VLQPSSVDSQTAMVLVNAIVFKGLWEKTFKDEDTQAMPFRVTEQESKPVQMMYQI
 GLFRVASMASEKMKILELPFASGTM
 SMLVLLPDEVSGLEQLESIINFEKLTEWTSSNVMEERKIKVYLPRMKMEEKYNLTS
 20 VLMAMGITDVFSSSANLSGISSAE
 SLKISQAVHAAHAEINEAGREVVGSAEAGVDAASVSEEFRAHPFLFCIKHIATNAV
 LFFGRCVSP

Other exemplary antigens

25 Exemplary antigens are epitopes of pathogenic microorganisms against which the host is defended by effector T cells responses, including CTL and delayed type hypersensitivity. These typically include viruses, intracellular parasites such as malaria, and bacteria that grow intracellularly such as *Mycobacterium* and *Listeria* species. Thus, the types of antigens included in the vaccine compositions of this invention may be any of
 30 those associated with such pathogens as well as tumor-specific antigens. It is noteworthy that some viral antigens are also tumor antigens in the case where the virus is a causative factor in the tumor.

In fact, the two most common cancers worldwide, hepatoma and cervical cancer, are associated with viral infection. Hepatitis B virus (HBV) (Beasley, R.P. *et al.*, *Lancet*
 35 2:1129-1133 (1981) has been implicated as etiologic agent of hepatomas. About 80-90% of cervical cancers express the E6 and E7 antigens (discussed above and exemplified herein) from one of four "high risk" human papillomavirus types: HPV-16, HPV-18, HPV-

31 and HPV-45 (Gissmann, L. *et al.*, *Ciba Found Symp.* 120:190-207, 1986; Beaudenon, S., *et al.* *Nature* 321:246-9, 1986, incorporated by reference herein). The HPV E6 and E7 antigens are the most promising targets for virus associated cancers in immunocompetent individuals because of their ubiquitous expression in cervical cancer. In addition to their
5 importance as targets for therapeutic cancer vaccines, virus-associated tumor antigens are also ideal candidates for prophylactic vaccines. Indeed, introduction of prophylactic HBV vaccines in Asia have decreased the incidence of hepatoma (Chang, MH *et al.* *New Engl. J. Med.* 336, 1855-1859 (1997), representing a great impact on cancer prevention.

Among the most important viruses in chronic human viral infections are HPV,
10 HBV, hepatitis C Virus (HCV), retroviruses such as human immunodeficiency virus (HIV-1 and HIV-2), herpes viruses such as Epstein Barr Virus (EBV), cytomegalovirus (CMV), HSV-1 and HSV-2, and influenza virus. Useful antigens include HBV surface antigen or HBV core antigen; ppUL83 or pp89 of CMV; antigens of gp120, gp41 or p24 proteins of HIV-1; ICP27, gD2, gB of HSV; or influenza hemagglutinin or nucleoprotein (Anthony, LS
15 *et al.*, *Vaccine* 1999; 17:373-83). Other antigens associated with pathogens that can be utilized as described herein are antigens of various parasites, including malaria, e.g., malaria peptide based on repeats of NANP.

In certain embodiments, the invention includes methods using foreign antigens in which individuals may have existing T cell immunity (such as influenza, tetanus toxin,
20 herpes etc). In other embodiments, the skilled artisan would readily be able to determine whether a subject has existing T cell immunity to a specific antigen according to well known methods available in the art and use a foreign antigen to which the subject does not already have an existing T cell immunity against.

In alternative embodiments, the antigen is from a pathogen that is a bacterium, such
25 as *Bordetella pertussis*; *Ehrlichia chaffeensis*; *Staphylococcus aureus*; *Toxoplasma gondii*; *Legionella pneumophila*; *Brucella suis*; *Salmonella enterica*; *Mycobacterium avium*; *Mycobacterium tuberculosis*; *Listeria monocytogenes*; *Chlamydia trachomatis*; *Chlamydia pneumoniae*; *Rickettsia rickettsii*; or, a fungus, such as, e.g., *Paracoccidioides brasiliensis*; or other pathogen, e.g., *Plasmodium falciparum*.

30 As used herein, the term “cancer” and includes, but is not limited to, solid tumors and blood borne tumors. The term cancer includes diseases of the skin, tissues, organs, bone, cartilage, blood and vessels. A term used to describe cancer that is far along in its growth, also referred to as “late stage cancer” or “advanced stage cancer,” is cancer that is

metastatic, e.g., cancer that has spread from its primary origin to another part of the body. In certain embodiments, advanced stage cancer includes stages 3 and 4 cancers. Cancers are ranked into stages depending on the extent of their growth and spread through the body; stages correspond with severity. Determining the stage of a given cancer helps doctors to
5 make treatment recommendations, to form a likely outcome scenario for what will happen to the patient (prognosis), and to communicate effectively with other doctors.

There are multiple staging scales in use. One of the most common ranks cancers into five progressively more severe stages: 0, I, II, III, and IV. Stage 0 cancer is cancer that is just beginning, involving just a few cells. Stages I, II, III, and IV represent progressively
10 more advanced cancers, characterized by larger tumor sizes, more tumors, the aggressiveness with which the cancer grows and spreads, and the extent to which the cancer has spread to infect adjacent tissues and body organs.

Another popular staging system is known as the TNM system, a three dimensional rating of cancer extensiveness. Using the TNM system, doctors rate the cancers they find
15 on each of three scales, where T stands for tumor size, N stands for lymph node involvement, and M stands for metastasis (the degree to which cancer has spread beyond its original locations). Larger scores on each of the three scales indicate more advanced cancer. For example, a large tumor that has not spread to other body parts might be rated T3, N0, M0, while a smaller but more aggressive cancer might be rated T2, N2, M1
20 suggesting a medium sized tumor that has spread to local lymph nodes and has just gotten started in a new organ location.

Cancers that may be treated by methods and compositions of the invention include, but are not limited to, cancer cells from the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestinal, gum, head, kidney, liver, lung, nasopharynx, neck, ovary,
25 prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to these: neoplasm, malignant; carcinoma; carcinoma, undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary
30 transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor,

malignant; branchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometroid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma w/squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; and robblastoma, malignant; sertoli cell carcinoma; leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malig melanoma in giant pigmented nevus; epithelioid cell melanoma; blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor, malignant; mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's

disease; Hodgkin's lymphoma; paraganuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; 5 lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia.

In addition to its applicability to human cancer and infectious diseases, the present invention is also intended for use in treating animal diseases in the veterinary medicine 10 context. Thus, the approaches described herein may be readily applied by one skilled in the art to treatment of veterinary herpes virus infections including equine herpes viruses, bovine viruses such as bovine viral diarrhea virus (for example, the E2 antigen), bovine herpes viruses, Marek's disease virus in chickens and other fowl; animal retroviral and lentiviral diseases (*e.g.*, feline leukemia, feline immunodeficiency, simian 15 immunodeficiency viruses, *etc.*); pseudorabies and rabies; and the like.

As for tumor antigens, any tumor-associated or tumor-specific antigen (or tumor cell derived epitope) (collectively, TAA) that can be recognized by T cells, including CTL, can be used. These include, without limitation, mutant p53, HER2/neu or a peptide thereof, or any of a number of melanoma-associated antigens such as MAGE-1, MAGE-3, 20 MART-1/Melan-A, tyrosinase, gp75, gp100, BAGE, GAGE-1, GAGE-2, GnT-V, and p15 (see, for example, US Pat. 6,187,306, incorporated herein by reference).

It is not necessary to include a full length antigen in a nucleic acid vaccine; it suffices to include a fragment that will be presented by MHC class I and/or II. A nucleic acid may include 1, 2, 3, 4, 5 or more antigens, which may be the same or different ones. 25

Approaches for Mutagenesis of E6, E7, and other Antigens

Mutants of the antigens described here may be created, for example, using the Quick Change Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA). Generally, antigens that may be used herein may be proteins or peptides that differ from the naturally- 30 occurring proteins or peptides but yet retain the necessary epitopes for functional activity. In certain embodiments, an antigen may comprise, consist essentially of, or consist of an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to that of the naturally-occurring antigen or a

fragment thereof. In certain embodiments, an antigen may also comprise, consist essentially of, or consist of an amino acid sequence that is encoded by a nucleotide sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to a nucleotide sequence encoding the naturally-

5 occurring antigen or a fragment thereof. In certain embodiments, an antigen may also comprise, consist essentially of, or consist of an amino acid sequence that is encoded by a nucleic acid that hybridizes under high stringency conditions to a nucleic acid encoding the naturally-occurring antigen or a fragment thereof. Hybridization conditions are further described herein.

10 In one embodiment, an exemplary protein may comprise, consist essentially of, or consist of, an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to that of a viral protein, including for example E6 or E7, such as an E6 or E7 sequence provided herein. Where the E6 or E7 protein is a detox E6 or E7 protein, the amino acid sequence of the protein may
15 comprise, consist essentially of, or consist of an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to that of an E6 or E7 protein, wherein the amino acids that render the protein a “detox” protein are present.

20 *Exemplary DNA vaccines encoding an Immunogenicity-Potentiating Polypeptide (IPP) and an antigen*

In one embodiment, a nucleic vaccine encodes a fusion protein comprising an antigen and a second protein, *e.g.*, an IPP. An IPP may act in potentiating an immune response by promoting: processing of the linked antigenic polypeptide via the MHC class I
25 pathway or targeting of a cellular compartment that increases the processing. This basic strategy may be combined with an additional strategy pioneered by the present inventors and colleagues, that involve linking DNA encoding another protein, generically termed a “targeting polypeptide,” to the antigen-encoding DNA. Again, for the sake of simplicity, the DNA encoding such a targeting polypeptide will be referred to herein as a “targeting
30 DNA.” That strategy has been shown to be effective in enhancing the potency of the vectors carrying only antigen-encoding DNA. See for example, the following PCT publications by Wu *et al*: WO 01/29233; WO 02/009645; WO 02/061113; WO 02/074920;

and WO 02/12281, all of which are incorporated by reference in their entirety. The other strategies include the use of DNA encoding polypeptides that promote or enhance:

- (a) development, accumulation or activity of antigen presenting cells or targeting of antigen to compartments of the antigen presenting cells leading to enhanced antigen presentation;
- (b) intercellular transport and spreading of the antigen; or
- (c) any combination of (a) and (b).
- (d) sorting of the lysosome-associated membrane protein type 1 (Sig/LAMP-1).

The strategy includes use of:

- (a) a viral intercellular spreading protein selected from the group of herpes simplex virus-1 VP22 protein, Marek's disease virus UL49 (see WO 02/09645 and US Patent No. 7,318,928), protein or a functional homologue or derivative thereof;
- (b) calreticulin (CRT) and other endoplasmic reticulum chaperone polypeptides selected from the group of CRT-like molecules ER60, GRP94, gp96, or a functional homologue or derivative thereof (see WO 02/12281 and US Patent No. 7,344,002);
- (c) a cytoplasmic translocation polypeptide domains of a pathogen toxin selected from the group of domain II of *Pseudomonas* exotoxin ETA or a functional homologue or derivative thereof (see published US application 20040086845);
- (d) a polypeptide that targets the centrosome compartment of a cell selected from γ -tubulin or a functional homologue or derivative thereof; or
- (e) a polypeptide that stimulates dendritic cell precursors or activates dendritic cell activity selected from the group of GM-CSF, Flt3-ligand extracellular domain, or a functional homologue or derivative thereof; or .
- (f) a costimulatory signal, such as a B7 family protein, including B7-DC (see U.S. Serial No. 09/794,210), B7.1, B7.2, soluble CD40, *etc.*).
- (g) an anti-apoptotic polypeptide selected from the group consisting of (1) BCL-xL, (2) BCL2, (3) XIAP, (4) FLICEc-s, (5) dominant-negative caspase-8, (6) dominant negative caspase-9, (7) SPI-6, and (8) a functional homologue or derivative of any of (1)-(7). (See WO 2005/047501).

The following publications, all of which are incorporated by reference in their entirety, describe IPPs: Kim TW *et al.*, *J Clin Invest* 112: 109-117, 2003; Cheng WF *et al.*, *J Clin Invest* 108: 669-678, 2001; Hung CF *et al.*, *Cancer Res* 61:3698-3703, 2001; Chen CH *et al.*, 2000, *supra*; US Pat. 6,734,173; published patent applications WO05/081716,

WO05/047501, WO03/085085, WO02/12281, WO02/074920, WO02/061113, WO02/09645, and WO01/29233. Comparative studies of these IPPs using HPV E6 as the antigen are described in Peng, S. *et al.*, *J Biomed Sci.* 12:689-700 2005.

An antigen may be linked N-terminally or C-terminally to an IPP. Exemplary IPPs
5 and fusion constructs encoding such are described below.

Lysosomal Associated Membrane Protein 1 (LAMP-1)

The DNA sequence encoding the E7 protein fused to the translocation signal sequence and LAMP-1 domain (Sig-E7-LAMP-1) [SEQ ID NO: 16] is:

10 ATGGCGGCCCCCGGCGCCCGGCGGCGCTGCTCCTGCTGCTGCTGGCAGGCCTT
GCACATGGCGCCTCAGCACTCTTTGAGGATCTAATCATGCATGGAGATACACCT
ACATTGCATGAATATATGTTAGATTTGCAACCAGAGACAACCTGATCTCTACTGT
TATGAGCAATTAAATGACAGCTCAGAGGAGGAGGATGAAATAGATGGTCCAGC
TGGACAAGCAGAACCGGACAGAGCCCATTACAATATTGTTACCTTTTGTGCAA
15 GTGTGACTCTACGCTTCGGTTGTGCGTACAAAGCACACACGTAGACATTCGTAC
TTTGGAAGACCTGTTAATGGGCACACTAGGAATTGTGTGCCCCATCTGTTCTCA
GGATCTTAACAACATGTTGATCCCCATTGCTGTGGGCGGTGCCCTGGCAGGGCT
GGTCCTCATCGTCCTCATTGCCTACCTCATTGGCAGGAAGAGGAGTCACGCCGG
CTATCAGACCATCTAG.

20 The amino acid sequence of Sig/E7/LAMP-1 [SEQ ID NO: 17] is:

MAAPGARRPL LLLLLAGLAH GASALFEDLI MHGDTPTLHE YMLDLQPETT
DLYCYEQLND SSEEDEIDG PAGQAEPDRA HYNIVTFCK CDSTLRCLVQ
STHVDIRTLE DLLMGTLGIV CPICSQDLNN MLIPIAVGGA LAGLVLIVLI
AYLIGRKRSY AGYQTI.

25 The nucleotide sequence of the immunogenic vector pcDNA3-Sig/E7/LAMP-1 [SEQ ID NO: 18] is shown below with the SigE7-LAMP-1 coding sequence in lower case and underscored:

GACGGATCGGGAGATCTCCCGATCCCCTATGGTCGACTCTCAGTACAATCTGCT
CTGATGCCGCATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTTGGAGGTCG
30 CTGAGTAGTGC GCGAGCAAAATTTAAGCTACAACAAGGCAAGGCTTGACCGA
CAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCGCGATGT
ACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATAGTAATC
AATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAA

CTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCATTGACG
TCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGT
CAATGGGTGGACTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGT
ATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCT
5 GGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCT
ACGTATTAGTCATCGCTATTACCATGGTGTGCGGTTTTGGCAGTACATCAA
TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCGAAGTCTCCACCCCATTTGA
CGTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGACTTTCGAAAATGTGCG
TAACAACCTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAG
10 GTCTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTT
ATCGAAATTAATACGACTCACTATAGGGAGACCCAAGCTGGCTAGCGTTTAAAC
GGGCCCTCTAGACTCGAGCGGCCGCCACTGTGCTGGATATCTGCAGAATTCa
tgggggccccggcgccccggcgccgctgctcctgctgctgctggcaggccttgacatggcgccctcagcactcttgag
gatctaatacatgcatggagatacacctacattgcatgaatatatgttagatttgcaaccagagacaactgatctctactg
15 ttatgagcaattaaatgacagctcagaggaggaggatgaaatagatgggtccagctggacaagcagaaccggacagagccc
attacaataattgttacctttttgttgcaagtgtgactctacgcttcggttgtgctgacaaagcacacacgtagacattcgt
actttggaagacctgttaatgggcacactaggaattgtgtgccccatctgttctcaggatcttaacaacatgttgatccc
cattgctgtggcggtgccctggcagggctggctcctcatcgtcctcattgcctacctcattggcaggaagaggagtcacg
ccggctatcagaccatctagGGATCCGAGCTCGGTACCAAGCTTAAGTTTAAACCGCTGAT
20 CAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGGCCCTCCCCCGT
GCCTTCCTTGACCTGGAAGGTGCCACTCCCCTGTCCTTTCCTAATAAAATGA
GGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGT
GGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGG
GATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGCTCTAG
25 GGGGTATCCCCACGCGCCCTGTAGCGGCGCATTAAAGCGCGGCGGGTGTGGTGG
TTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCG
CTTCTCTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCTCCGTCGAAGCTCTAAAT
CGGGGCATCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAA
AACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTT
30 TTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAA
CTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTT
GGGGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGC
GAATTAATTCTGTGGAATGTGTGTCAGTTAGGGTGTGGAAAGTCCCCAGGCTCC

CCAGGCAGGCAGAAAGTATGCAAAGCATGCATCTCAATTAGTCAGCAACCAGGT
GTGGAAAGTCCCCAGGCTCCCCAGCAGGCAGAAAGTATGCAAAGCATGCATCTC
AATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACT
CCGCCCAGTTCGCCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATG
5 CAGAGGCCGAGGCCGCCTCTGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGC
TTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTCCCGGGAGCTTGTATATCCATTT
TCGGATCTGATCAAGAGACAGGATGAGGATCGTTTCGCATGATTGAACAAGAT
GGATTGCACGCAGGTTCTCCGGCCGCTTGGGTGGAGAGGCTATTCGGCTATGAC
TGGGCACAACAGACAATCGGCTGCTCTGATGCCGCCGTGTTCCGGCTGTCAGCG
10 CAGGGGCGCCCGGTTCTTTTTGTCAAGACCGACCTGTCCGGTGGCCTGAATGAA
CTGCAGGACGAGGCAGCGCGGCTATCGTGGCTGGCCACGACGGGCGTTCCTTG
CGCAGCTGTGCTCGACGTTGTCACTGAAGCGGGAAGGGACTGGCTGCTATTGGG
CGAAGTGCCGGGGCAGGATCTCCTGTCTCATCTCACCTTGCTCCTGCCGAGAAAGT
ATCCATCATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTG
15 CCCATTCGACCACCAAGCGAAACATCGCATCGAGCGAGCACGTA CTGGATGG
AAGCCGGTCTTGTCGATCAGGATGATCTGGACGAAGAGCATCAGGGGCTCGCG
CCAGCCGAACTGTTCCGCCAGGCTCAAGGCGCGCATGCCCGACGGCGAGGATCT
CGTCGTGACCCATGGCGATGCCTGCTTGCCGAATATCATGGTGGAAAATGGCCG
CTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTGGCGGACCGCTATCAGGA
20 CATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGCGAATGGGCTGA
CCGCTTCCTCGTGCTTTACGGTATCGCCGCTCCCGATTTCGCAGCGCATCGCCTTC
TATCGCCTTCTTGACGAGTTCTTCTGAGCGGGACTCTGGGGTTCGAAATGACC
GACCAAGCGACGCCCAACCTGCCATCACGAGATTTTCGATTCCACCGCCGCCTTC
TATGAAAGGTTGGGCTTCGGAATCGTTTTCCGGGACGCCGGCTGGATGATCCTC
25 CAGCGCGGGGATCTCATGCTGGAGTTCTTCGCCCACCCCAACTTGTTTATTG
CAGCTTATAATGGTTACAAATAAAGCAATAGCATCACAAATTTACAAATAAA
GCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCTT
ATCATGTCTGTATACCGTCGACCTCTAGCTAGAGCTTGGCGTAATCATGGTC
ATAGCTGTTTCCTGTGTGAAATTGTTATCCGCTCACAATTCACACAACATACG
30 AGCCGGAAGCATAAAGTGTAAGCCTGGGGTGCCTAATGAGTGAGCTAACTCA
CATTAAATTGCGTTGCGCTCACTGCCCCGCTTTCAGTCGGGAAACCTGTCGTGC

CAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGC GTATTGG
GCGCTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCCGGCTGCGG
CGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAG
GGGATAACGCAGGAAAGAACATGTGAGCAAAAAGGCCAGCAAAAAGGCCAGGAA
5 CCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCTGACGA
GCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTAT
AAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGA
CCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCT
TTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTTCGCTCCAAG
10 CTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGT
AACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCA
GCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTT
CTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTATTTGGTATCTG
CGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGG
15 CAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTTGTTTGCAAGCAGCAGATTAC
GCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGA
CGCTCAGTGGAACGAAAACCTCACGTTAAGGGATTTTGGTCATGAGATTATCAAA
AAGGATCTTCACCTAGATCCTTTTAAATTAATAAATGAAGTTTTAAATCAATCTA
AAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGC
20 ACCTATCTCAGCGATCTGTCTATTTTCGTTTCATCCATAGTTGCCTGACTCCCCGTC
GTGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATG
ATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCA
GCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAG
TCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTTCGCCAGTTAATAGTTTG
25 CGCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTACGCTCGTCGTTTGGT
ATGGCTTCATTACAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCC
ATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGT
AAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTT
ACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAG
30 TCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATA
CGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAA
ACGTTCTTCGGGGCGAAAACCTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTC
GATGTAACCCACTCGTGACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGC

GTTTCTGGGTGAGCAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAA
 GGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAA
 GCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGA
 AAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGAC
 5 GTC,

HSP70 from M. tuberculosis

The nucleotide sequence encoding HSP70 (SEQ ID NO: 19) is (nucleotides 10633-12510 of the *M. tuberculosis* genome in GenBank [NC_000962](#)):

10 atggctcg tgcggtcggg atcgacctcg ggaccacca ctccgtcgtc tcggttctgg aaggtggcga cccggtcgtc
 gtcgccaact ccgaggggtc caggaccacc ccgtcaattg tcgcgttcgc ccgcaacggt gaggtgctgg tcggccagcc
 cgccaagaac caggcagtga ccaacgtcga tcgcacctg cgtcgggtca agcgacacat gggcagcgac
 tgggtccatag agattgacgg caagaaatac accgcgccgg agatcagcgc ccgcattctg atgaagctga agcgcgacgc
 cgaggcctac ctccgtgagg acattaccga cgcgggtatc acgacgccc cctactcaa tgacgccag cgtcaggcca
 15 ccaaggacgc cggccagatc gccggcctca acgtgctgcg gatcgtcaac gagccgaccg cggccgcgt
 ggcctacggc ctgcacaagg gcgagaagga gcagcgaatc ctggtcttcg acttgggtgg tggcatttc gacgtttccc
 tgctggagat cggcgagggt gtggtgagg tccgtgccac ttcgggtgac aaccacctcg gcggcgacga ctgggaccag
 cgggtcgtcg attggtggt ggacaagtc aagggcacca gcggcatcga tctgaccaag gacaagatgg cgatgcagcg
 gctgcgggaa gccgccgaga aggcaaat cgagctgagt tcgagtcagt ccacctgat caacctgcc tacataccg
 20 tcgacgccga caagaaccg ttgttcttag acgagcagct gaccgcgcg gattccaac ggatcactca ggacctgctg
 gaccgcactc gcaagccgtt ccagtcggtg atcgctgaca ccggcatttc ggtgtcggag atcgatcac ttgtgtcgt
 ggggtggtcg acccggtgc ccgcggtgac cgatctggtc aaggaactca ccggcggcaa ggaacccaac
 aaggcgctca acccgatga ggtgtcgcg gtgggagccg ctctgcagc cggcgtctc aaggcgagg
 tgaaagacgt tctgtctt gatgttacc cgctgagcct gggtatcgag accaaggcg gggatgatgac caggtcatc
 25 gagcgcaaca ccacgatccc caccaagcgg tcggagactt tcaccaccgc cgacgacaac caaccgtcg
 tgcatatcca ggtctatcag ggggagcgtg agatcgccgc gcacaacaag ttgctcgggt ccttcgagct gaccggcatc
 ccgccggcgc cgcgggggat tccgagatc gaggtcatt tcgacatga cgcaacggc attgtgcag tcaccgcaa
 ggacaagggc accggcaagg agaacacgat ccgaatccag gaaggctcgg gcctgtcaa ggaagacatt
 gaccgatga tcaaggacgc cgaagcgac gccgaggagg atcgcaagcg tcgcgaggag gccgatgttc
 30 gtaatcaag cgagacattg gtctaccaga cggagaagt cgtaaagaa cagcgtgagg ccgagggtgg ttcgaagta
 cctgaagaca cgtgaacaa ggtgatgcc gcggtggcgg aagcgaaggc ggcacttggc ggatcggata ttccggccat
 caagtcggcg atggagaagc tgggccagga gtcgcaggct ctggggcaag cgatctacga agcagctcag

gctgcgtcac aggccactgg cgtgcccac cccggcggcg agccggggcg tgcccacccc ggctcggctg
atgacgttgt ggacgcggag gtggtcgacg acggccggga ggccaagtga

The amino acid sequence of HSP70 [SEQ ID NO: 20] is:

MARAVGIDLG TTNSVSVLE GGDPVVVANS EGSRTTPSIV AFARNGEVLV
5 GQPAKNQAVT NVDRTVRSVK RHMGS DWSIE IDGKKYTAPE ISARILMKLK
RDAEAYLGED ITDAVITTPA YFNDAQRQAT KDAGQIAGLN VLRIVNEPTA
AALAYGLDKG EKEQRILVFD LGGGTDFVSL LEIGEGVVEV RATSGDNHLG
GDDWDQRVVD WLVDKFKGTS GIDLT KD KMA MQRLREAAEK AKIELSSSQS
TSINLPYITV DADKNPLFLD EQLTRA EFQR ITQDLLDRTR KPFQSVIADT
10 GISVSEIDHV VLVGGSTRMP AVTDLVKELT GGKEPNKGVN PDEVVAVGAA
LQAGVLKGEV KDVLLLDVTP LSLGIETKGG VMTRLIERNT TIPTKRSETF
TTADDNQPSV QIQVYQGERE IAAHNKLLGS FELTGIPPAP RGIPQIEVTF
DIDANGIVHV TAKDKGTGKE NTIRIQEGSG LSKEDIDRMI KDAEAHAED
RKRREEADV R NQAETLVYQT EK FVKEQREA EGGSKVPEDT LNKVDA AVAE
15 AKAALGGSDI SAIKSAMEKL GQESQALGQA IYEAAQAASQ ATGA AHPGGE
PGGAHPGSAD DVVDAEVVDD GREAK

The E7-Hsp70 chimera/fusion polypeptide sequences (Nucleotide sequence SEQ ID NO: 21 and amino acid sequence SEQ ID NO: 22) are provided below. The E7 coding sequence is shown in upper case and underscored.

20 1/1 31/11
ATG CAT GGA GAT ACA CCT ACA TTG CAT GAA TAT ATG TTA GAT TTG CAA
CCA GAG ACA ACT
Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr Thr
61/21 91/31
25 GAT CTC TAC TGT TAT GAG CAA TTA AAT GAC AGC TCA GAG GAG GAG GAT
GAA ATA GAT GGT
Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser Glu Glu Glu Asp Glu Ile Asp Gly
121/41 151/51
CCA GCT GGA CAA GCA GAA CCG GAC AGA GCC CAT TAC AAT ATT GTA ACC
30 TTT TGT TGC AAG
Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys
181/61 211/71
TGT GAC TCT ACG CTT CGG TTG TGC GTA CAA AGC ACA CAC GTA GAC ATT
CGT ACT TTG GAA
35 Cys Asp Ser Thr Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu
241/81 271/91
GAC CTG TTA ATG GGC ACA CTA GGA ATT GTG TGC CCC ATC TGT TCT CAA
GGA TCC atg gct
Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln Gly Ser Met *ala*
40 301/101 331/111

cgt gcg gtc ggg atc gac ctc ggg acc acc aac tcc gtc gtc tcg gtt ctg gaa ggt ggc
 Arg Ala Val Gly Ile Asp Leu Gly Thr Thr Asn Ser Val Val Ser Val Leu Glu Gly Gly
 361/121 391/131
 gac ccg gtc gtc gtc gcc aac tcc gag ggc tcc agg acc acc ccg tca att gtc gcg ttc
 5 Asp Pro Val Val Val Ala Asn Ser Glu Gly Ser Arg Thr Thr Pro Ser Ile Val Ala Phe
 421/141 451/151
 gcc cgc aac ggt gag gtg ctg gtc ggc cag ccc gcc aag aac cag gca gtg acc aac gtc
 Ala Arg Asn Gly Glu Val Leu Val Gly Gln Pro Ala Lys Asn Gln Ala Val Thr Asn Val
 481/161 511/171
 10 gat cgc acc gtg cgc tcg gtc aag cga cac atg ggc agc gac tgg tcc ata gag att gac
 Asp Arg Thr Val Arg Ser Val Lys Arg His Met Gly Ser Asp Trp Ser Ile Glu Ile Asp
 541/181 571/191
 ggc aag aaa tac acc gcg ccg gag atc agc gcc cgc att ctg atg aag ctg aag cgc gac
 Gly Lys Lys Tyr Thr Ala Pro Glu Ile Ser Ala Arg Ile Leu Met Lys Leu Lys Arg Asp
 15 601/201 631/211
 gcc gag gcc tac ctc ggt gag gac att acc gac gcg gtt atc acg acg ccc gcc tac ttc
 Ala Glu Ala Tyr Leu Gly Glu Asp Ile Thr Asp Ala Val Ile Thr Thr Pro Ala Tyr Phe
 661/221 691/231
 aat gac gcc cag cgt cag gcc acc aag gac gcc ggc cag atc gcc ggc ctc aac gtg ctg
 20 Asn Asp Ala Gln Arg Gln Ala Thr Lys Asp Ala Gly Gln Ile Ala Gly Leu Asn Val Leu
 721/241 751/251
 cgg atc gtc aac gag ccg acc gcg gcc gcg ctg gcc tac ggc ctc gac aag ggc gag aag
 Arg Ile Val Asn Glu Pro Thr Ala Ala Ala Leu Ala Tyr Gly Leu Asp Lys Gly Glu Lys
 781/261 811/271
 25 gag cag cga atc ctg gtc ttc gac ttg ggt ggt ggc act ttc gac gtt tcc ctg ctg gag
 Glu Gln Arg Ile Leu Val Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser Leu Leu Glu
 841/281 871/291
 atc ggc gag ggt gtg gtt gag gtc cgt gcc act tcg ggt gac aac cac ctc ggc ggc gac
 Ile Gly Glu Gly Val Val Glu Val Arg Ala Thr Ser Gly Asp Asn His Leu Gly Gly Asp
 30 901/301 931/311
 gag tgg gac cag cgg gtc gtc gat tgg ctg gtg gac aag ttc aag ggc acc agc ggc atc
 Asp Trp Asp Gln Arg Val Val Asp Trp Leu Val Asp Lys Phe Lys Gly Thr Ser Gly Ile
 961/321 991/331
 gat ctg acc aag gac aag atg gcg atg cag cgg ctg cgg gaa gcc gcc gag aag gca aag
 35 Asp Leu Thr Lys Asp Lys Met ala Met Gln Arg Leu Arg Glu Ala Ala Glu Lys Ala Lys
 1021/341 1051/351
 atc gag ctg agt tcg agt cag tcc acc tcg atc aac ctg ccc tac atc acc gtc gac gcc
 Ile Glu Leu Ser Ser Ser Gln Ser Thr Ser Ile Asn Leu Pro Tyr Ile Thr Val Asp Ala
 1081/361 1111/371
 40 gac aag aac ccg ttg ttc tta gac gag cag ctg acc cgc gcg gag ttc caa cgg atc act
 Asp Lys Asn Pro Leu Phe Leu Asp Glu Gln Leu Thr Arg Ala Glu Phe Gln Arg Ile Thr
 1141/381 1171/391
 cag gac ctg ctg gac cgc act cgc aag ccg ttc cag tcg gtg atc gct gac acc ggc att
 Gln Asp Leu Leu Asp Arg Thr Arg Lys Pro Phe Gln Ser Val Ile Ala Asp Thr Gly Ile
 45 1201/401 1231/411
 tcg gtg tcg gag atc gat cac gtt gtg ctc gtg ggt ggt tcg acc cgg atg ccc gcg gtg
 Ser Val Ser Glu Ile Asp His Val Val Leu Val Gly Gly Ser Thr Arg Met Pro Ala Val
 1261/421 1291/431
 acc gat ctg gtc aag gaa ctc acc ggc ggc aag gaa ccc aac aag ggc gtc aac ccc gat

Thr Asp Leu Val Lys Glu Leu Thr Gly Gly Lys Glu Pro Asn Lys Gly Val Asn Pro Asp
 1321/441 1351/451
 gag gtt gtc gcg gtg gga gcc gct ctg cag gcc ggc gtc ctc aag ggc gag gtg aaa gac
 Glu Val Val Ala Val Gly Ala Ala Leu Gln Ala Gly Val Leu Lys Gly Glu Val Lys Asp
 5 1381/461 1411/471
 gtt ctg ctg ctt gat gtt acc ccg ctg agc ctg ggt atc gag acc aag ggc ggg gtg atg
 Val Leu Leu Leu Asp Val Thr Pro Leu Ser Leu Gly Ile Glu Thr Lys Gly Gly Val Met
 1441/481 1471/491
 acc agg ctc atc gag cgc aac acc acg atc ccc acc aag cgg tcg gag act ttc acc acc
 10 Thr Arg Leu Ile Glu Arg Asn Thr Thr Ile Pro Thr Lys Arg Ser Glu Thr Phe Thr Thr
 1501/501 1531/511
 gcc gac gac aac caa ccg tcg gtg cag atc cag gtc tat cag ggg gag cgt gag atc gcc
 Ala Asp Asp Asn Gln Pro Ser Val Gln Ile Gln Val Tyr Gln Gly Glu Arg Glu Ile Ala
 1561/521 1591/531
 15 gcg cac aac aag ttg ctc ggg tcc ttc gag ctg acc ggc atc ccg ccg gcg ccg cgg ggg
 Ala His Asn Lys Leu Leu Gly Ser Phe Glu Leu Thr Gly Ile Pro Pro Ala Pro Arg Gly
 1621/541 1651/551
 att ccg cag atc gag gtc act ttc gac atc gac gcc aac ggc att gtg cac gtc acc gcc
 Ile Pro Gln Ile Glu Val Thr Phe Asp Ile Asp Ala Asn Gly Ile Val His Val Thr Ala
 20 1681/561 1711/571
 aag gac aag ggc acc ggc aag gag aac acg atc cga atc cag gaa ggc tcg ggc ctg tcc
 Lys Asp Lys Gly Thr Gly Lys Glu Asn Thr Ile Arg Ile Gln Glu Gly Ser Gly Leu Ser
 1741/581 1771/591
 aag gaa gac att gac cgc atg atc aag gac gcc gaa gcg cac gcc gag gag gat cgc aag
 25 Lys Glu Asp Ile Asp Arg Met Ile Lys Asp Ala Glu Ala His Ala Glu Glu Asp Arg Lys
 1801/601 1831/611
 cgt cgc gag gag gcc gat gtt cgt aat caa gcc gag aca ttg gtc tac cag acg gag aag
 Arg Arg Glu Glu Ala Asp Val Arg Asn Gln Ala Glu Thr Leu Val Tyr Gln Thr Glu Lys
 1861/621 1891/631
 30 ttc gtc aaa gaa cag cgt gag gcc gag ggt ggt tcg aag gta cct gaa gac acg ctg aac
 Phe Val Lys Glu Gln Arg Glu Ala Glu Gly Gly Ser Lys Val Pro Glu Asp Thr Leu Asn
 1921/641 1951/651
 aag gtt gat gcc gcg gtg gcg gaa gcg aag gcg gca ctt ggc gga tcg gat att tcg gcc
 Lys Val Asp Ala Ala Val Ala Glu Ala Lys Ala Ala Leu Gly Gly Ser Asp Ile Ser Ala
 35 1981/661 2011/671
 atc aag tcg gcg atg gag aag ctg ggc cag gag tcg cag gct ctg ggg caa gcg atc tac
 Ile Lys Ser Ala Met Glu Lys Leu Gly Gln Glu Ser Gln Ala Leu Gly Gln Ala Ile Tyr
 2041/681 2071/691
 gaa gca gct cag gct gcg tea cag gcc act ggc gct gcc cac ccc ggc tcg gct gat gaA
 40 GLU ALA ALA GLN ALA ALA SER GLN ALA THR GLY ALA ALA HIS PRO GLY
 SER ALA ASP GLU
 2101/701
 AGC a
 Ser.
 45

ETA(dII) from Pseudomonas aeruginosa

The complete coding sequence for *Pseudomonas aeruginosa* exotoxin type A (ETA) - SEQ ID NO: 23 - GenBank Accession No. K01397, is shown below:

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ctgcagctgg tcagccggtt tccgcaacgc ttgaagtctt ggccgatata cggcagggc cagccatcgt tcgacgaata
5 aagccacctc agccatgatg ccccttccat cccagcgga accccgacat ggacgcaaa gccctgctcc tcggcagcct
ctgcctggcc gcccattcg cggacgggc gacgctcgac aatgctctct ccgctgcct cggcgccgg ctcggtgcac
cgcacacggc ggagggccag ttgcacctgc cactcaccct ttagggccgg cgctccaccg gcgaatggcg
ctgtacctcg gcgctggtgc gatctgggt gctggccagg ggcgacagc cggacagcct cgtgctcaa gagggctgct
cgatagtcgc caggacacgc cgcgcacgct gacctggcg gcggacgcc gcttggcgag cggccgcgaa
10 ctggtcgtca cctggggtg tcagggcct gactgacagg cggggtgcc accaccagg cgagatggac gccctgcatg
tactctccga tcggcaagcc tccggtcgc acattacca ctctgcaatc cagttcataa atcccataa agccctcttc
cgctccccgc cagcctcccc gcatcccgca cctagacgc cccgccgctc tccgccggct cgcccgacaa
gaaaaaccaa ccgctcgatc agcctcatcc ttcaccatc acaggagcca tcgcatgca cctgataccc cattgcatc
cctggtcgc cagcctggc ctgctgcgc gggctcgtc cgcgtccgc gccgaggaag cctcgacct ctggaacgaa
15 tgcgcaaag cctgcgtgct cgacctcaag gacggcgtgc gttccagcc catgagcgtc gaccggcca tcgccgacac
caacggccag ggcgtgctgc actactccat ggtctggag ggcggcaac acgcgctcaa gctggccatc
gacaacgccc tcagcatcac cagcgacggc ctgacctcc gcctcgaagg cggcgtcgag ccgaacaagc
cggctcgcta cagctacacg cgccaggcgc gcggcagttg gtcgtgaac tggctggtac cgtcggcca
cgagaagccc tcgaacatca aggtgttcac ccacgaactg aacgccggca accagctcag ccacatgctc ccgatctaca
20 ccatcgagat gggcgacgag ttgctggcga agctggcgc cgtgccacc ttctcgtca gggcgcacga
gagcaacgag atgcagccga cgtcgccat cagccatgcc ggggtcagcg tggctatggc ccagaccag
ccgcgccggg aaaagcgtg gagcgaatgg gccagcgga aggtgttggt cctgctcgac ccgctggacg
gggtctaaa ctacctgcc cagcaacgct gcaacctga cgtacctgg gaaggcaaga tctaccgggt gtcgccggc
aaccggcgga agcatgacct ggacatcaa cccacggtca tcagtcacg cctgacttt cccgagggcg gcagcctggc
25 cgcgctgacc gcgcaccagg cttgccacct gccgctggag actttaccc gtcacgcca gccgcgcggc tgggaacaac
tggagcagtg cggctatccg gtgcagcggc tggctgccct ctacctggcg gcgcggctgt cgtggaacca ggtcgaccag
gtgatccga acgacctggc cagccccggc agcggcggcg acctggcgga agcgatccgc gagcagccgg
agcaggcccc tctggccctg acctggccg ccgccgagag cgagcgcttc gtccggcagg gcaccggcaa
cgacgaggcc ggcgcggcca acgccgacgt ggtgagcctg acctgcccgg tcgccgccgg tgaatgcgcg
30 gggccggcgg acagcgcgga cgccctgctg gagcgcaact atccactgg cgcggagttc ctcggcgacg
ggcgcgacgt cagcttcagc acccgcgga cgcagaactg gacggtggag cggtgctcc aggcgcaccg
ccaactggag gagcgcggt atgtgtctg cggctaccac ggcaccttc tcgaagcggc gaaagcatc gtcttcggcg
gggtgcgcgc gcgcagccag gacctgacg cgtatggcg cggttctat atcccgcgat atccggcgct ggccacggc

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tacgcccagg accaggaacc cgacgcacgc ggccggatcc gcaacggtgc cctgctgcgg gtctatgtgc
 cgcgctcgag cctgccgggc ttctaccgca ccagcctgac cctggccgcg ccggaggcgg cgggcgaggt
 cgaacggctg atcgccatc cgctgccgt ggcctggac gccataccg gccccgagga ggaaggcggg
 cgcctggaga ccattctcg ctggccgtg gccgagcgca ccgtggtgat tcctcgggc atccccaccg acccgcgaa
 5 cgtcgggcggc gacctgacc cgtccagcat ccccgacaag gaacaggcga tcagcgcct gccggactac
 gccagccagc ccggcaaacc gccgcgcgag gacctgaagt aactgccgcg accggccggc tccctcgca
 ggagccggcc ttctggggc ctggccatac atcaggtttt cctgatgcca gccaatga atatgaattc 2760

The amino acid sequence of ETA (SEQ ID NO: 24), GenBank Accession No. K01397, is:

10 *MHLIPHWIPL VASLGLLAGG SSASA**A**EEAF DLWNECAKAC VLDLKDGVRS*
SRMSVDPAIA DTNGQGVLYH SMVLEGGNDA LKLAIDNALS ITSDGLTIRL
EGGVEPNKPV RYSYTRQARG SWSLNWLVI GHEKPSNIKV FIHELNAGNQ
LSHMSPIYTI EMGDELLAKL ARDATFFVRA HESNEMQPTL AISHAGVSVV
MAQTQPRREK RWSEWASGKV LCLLDPLDGV YNYLAQQRCN LDDTWEGKIY
 15 *RVLAGNPAKH DLDIKPTVIS HRLHFPEGGS LAALTAHQAC HLPLETFTRH*
RQPRGWEQLE QCGYPVQRLV ALYLAARLSW NQVDQVIRNA LASPGSGGDL
GEAIREQPEQ ARLALTLAAA ESERFVRQGT GNDEAGAANA DVVSLTCPVA
AGECAGPADS GDALLERNYP TGAEFLGDGG DVSFSTRGTQ NWTVERLLQA
HRQLEERGYV FVGYPHGTFL AAQSIVFGGV RARSQDLDAI WRGFYIAGDP
 20 *ALAYGYAQDQ EPDARGRIRN GALLRVYVPR SSLPGFYRTS LTLAAPEAAG*
EVERLIGHPL PLRLDAITGP EEGGRLETI LGWPLAERTV VIPSAIPTDP
RNVGGDLDP SIPDKEQAIS ALPDYASQPG KPPREDLK 638

Residues 1-25 (italicized) above represent the signal peptide. The first residue of the mature polypeptide, Ala, is bolded/underscored. The mature polypeptide is residues 26-638 of SEQ ID NO: 24.

Domain II (ETA(II)), translocation domain (underscored above) spans residues 247-417 of the mature polypeptide (corresponding to residues 272-442 of SEQ ID NO: 24) and is presented below separately as SEQ ID NO: 25.

RLHFPEGGS LALTAHQACH LPLETFTRHR QPRGWEQLEQ CGYPVQRLVA
 30 LYLAARLSWN QVDQVIRNAL ASPGSGGDLG EAIREQPEQA RLALTLAAAE
 SERFVRQGTG NDEAGAANAD VVSLTCPVAA GECAGPADSG DALLERNYPT
 GAEFLGDGGD VSFSTRGTQN W 171

The construct in which ETA(dII) is fused to HPV-16 E7 is shown below (nucleotides; SEQ ID NO: 26 and amino acids; SEQ ID NO: 27). The ETA(dII) sequence appears in plain font, extra codons from plasmid pcDNA3 are italicized. Nucleotides between ETA(dII) and E7 are also bolded (and result in the interposition of two amino acids between ETA(dII) and E7). The E7 amino acid sequence is underscored (ends with Gln at position 269).

```

1/1                                     31/11
atg cgc ctg cac ttt ccc gag ggc ggc agc ctg gcc gcg ctg acc
gcg cac cag gct tgc
10 Met arg leu his phe pro glu gly gly ser leu ala ala leu thr
ala his gln ala cys
61/21                                     91/31
cac ctg ccg ctg gag act ttc acc cgt cat cgc cag ccg cgc ggc
tgg gaa caa ctg gag
15 His Leu Pro Leu Glu Thr Phe Thr Arg His Arg Gln Pro Arg Gly
Trp Glu Gln Leu Glu
121/41                                     151/51
cag tgc ggc tat ccg gtg cag cgg ctg gtc gcc ctc tac ctg gcg
gcg cgg ctg tcg tgg
20 Gln Cys Gly Tyr Pro Val Gln Arg Leu Val Ala Leu Tyr Leu Ala
Ala Arg Leu Ser Trp
181/61                                     211/71
aac cag gtc gac cag gtg atc cgc aac gcc ctg gcc agc ccc ggc
agc ggc ggc gac ctg
25 Asn Gln Val Asp Gln Val Ile Arg Asn Ala Leu Ala Ser Pro Gly
Ser Gly Gly Asp Leu
241/81                                     271/91
ggc gaa gcg atc cgc gag cag ccg gag cag gcc cgt ctg gcc ctg
acc ctg gcc gcc gcc
30 Gly Glu Ala Ile Arg Glu Gln Pro Glu Gln Ala Arg Leu Ala Leu
Thr Leu Ala Ala Ala
301/101                                     331/111
gag agc gag cgc ttc gtc cgg cag ggc acc ggc aac gac gag gcc
ggc gcg gcc aac gcc
35 Glu Ser Glu Arg Phe Val Arg Gln Gly Thr Gly Asn Asp Glu Ala
Gly Ala Ala Asn Ala
361/121                                     391/131
gac gtg gtg agc ctg acc tgc ccg gtc gcc gcc ggt gaa tgc gcg
ggc ccg gcg gac agc
40 Asp Val Val Ser Leu Thr Cys Pro Val Ala Ala Gly Glu Cys Ala
Gly Pro Ala Asp Ser
421/141                                     451/151
ggc gac gcc ctg ctg gag cgc aac tat ccc act ggc gcg gag ttc
ctc ggc gac ggc ggc
45 Gly Asp Ala Leu Leu Glu Arg Asn Tyr Pro Thr Gly Ala Glu Phe
Leu Gly Asp Gly Gly
481/161                                     511/171
gac gtc agc ttc agc acc cgc ggc acg cag aac gaa ttc atg cat
gga gat aca cct aca

```

Asp Val Ser Phe Ser Thr Arg Gly Thr Gln **Asn Glu Phe** Met His
Gly Asp Thr Pro Thr
 541/181 571/191
 5 ttg cat gaa tat atg tta gat ttg caa cca gag aca act gat ctc
 tac tgt tat gag caa
 Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr Thr Asp Leu
Tyr Cys Tyr Glu Gln
 601/201 631/211
 10 tta aat gac agc tca gag gag gag gat gaa ata gat ggt cca gct
 gga caa gca gaa ccg
 Leu Asn Asp Ser Ser Glu Glu Glu Asp Glu Ile Asp Gly Pro Ala
Gly Gln Ala Glu Pro
 661/221 691/231
 15 gac aga gcc cat tac aat att gta acc ttt tgt tgc aag tgt gac
 tct acg ctt cgg ttg
 Asp Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp
Ser Thr Leu Arg Leu
 721/241 751/251
 20 tgc gta caa agc aca cac gta gac att cgt act ttg gaa gac ctg
 tta atg ggc aca cta
 Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu Asp Leu
Leu Met Gly Thr Leu
 781/261 811/271
 25 gga att gtg tgc ccc atc tgt tct caa gga tcc gag ctc ggt acc
 aag ctt aag ttt aaa
 Gly Ile Val Cys Pro Ile Cys Ser Gln Gly Ser Glu Leu Gly Thr
Lys Leu Lys Phe Lys
 841/281
 30 ccg ctg atc agc ctc gac tgt gcc ttc tag

Pro Leu Ile Ser Leu Asp Cys Ala Phe AMB

The nucleotide sequence of the pcDNA3 vector encoding E7 and HSP70 (pcDNA3-E7-Hsp70) (SEQ ID NO: 3).

35 atg acc tct cgc cgc tcc gtg aag tcg ggt ccg cgg gag gtt ccg cgc
 48
 Met Thr Ser Arg Arg Ser Val Lys Ser Gly Pro Arg Glu Val Pro Arg
 1 5 10 15
 40 gat gag tac gag gat ctg tac tac acc ccg tct tca ggt atg gcg agt
 96
 Asp Glu Tyr Glu Asp Leu Tyr Tyr Thr Pro Ser Ser Gly Met Ala Ser
 20 25 30
 45 ccc gat agt ccg cct gac acc tcc cgc cgt ggc gcc cta cag aca cgc
 144
 Pro Asp Ser Pro Pro Asp Thr Ser Arg Arg Gly Ala Leu Gln Thr Arg
 35 40 45
 50 tcg cgc cag agg ggc gag gtc cgt ttc gtc cag tac gac gag tcg gat
 192
 Ser Arg Gln Arg Gly Glu Val Arg Phe Val Gln Tyr Asp Glu Ser Asp
 50 55 60
 55 tat gcc ctc tac ggg ggc tcg tct tcc gaa gac gac gaa cac ccg gag
 240
 Tyr Ala Leu Tyr Gly Gly Ser Ser Ser Glu Asp Asp Glu His Pro Glu

	65				70					75				80		
	gtc	ccc	cgg	acg	cgg	cgt	ccc	ggt	tcc	ggg	gcg	ggt	ttg	tcc	ggc	cgc
5	Val	Pro	Arg	Thr	Arg	Arg	Pro	Val	Ser	Gly	Ala	Val	Leu	Ser	Gly	Pro
	288				85					90				95		
	ggg	cct	gcg	cgg	gcg	cct	ccg	cca	ccc	gct	ggg	tcc	gga	ggg	gcc	gga
10	Gly	Pro	Ala	Arg	Ala	Pro	Pro	Pro	Pro	Ala	Gly	Ser	Gly	Gly	Ala	Gly
	336			100					105					110		
	cgc	aca	ccc	acc	acc	gcc	ccc	cgg	gcc	ccc	cga	acc	cag	cgg	gtg	gcg
15	Arg	Thr	Pro	Thr	Thr	Ala	Pro	Arg	Ala	Pro	Arg	Thr	Gln	Arg	Val	Ala
	384		115					120					125			
	tct	aag	gcc	ccc	gcg	gcc	ccg	gcg	gcg	gag	acc	acc	cgc	ggc	agg	aaa
20	Ser	Lys	Ala	Pro	Ala	Ala	Pro	Ala	Ala	Glu	Thr	Thr	Arg	Gly	Arg	Lys
	432	130					135					140				
	tcg	gcc	cag	cca	gaa	tcc	gcc	gca	ctc	cca	gac	gcc	ccc	gcg	tcg	acg
25	Ser	Ala	Gln	Pro	Glu	Ser	Ala	Ala	Leu	Pro	Asp	Ala	Pro	Ala	Ser	Thr
	480	145				150					155				160	
	gcg	cca	acc	cga	tcc	aag	aca	ccc	gcg	cag	ggg	ctg	gcc	aga	aag	ctg
30	Ala	Pro	Thr	Arg	Ser	Lys	Thr	Pro	Ala	Gln	Gly	Leu	Ala	Arg	Lys	Leu
	528				165					170					175	
	cac	ttt	agc	acc	gcc	ccc	cca	aac	ccc	gac	gcg	cca	tgg	acc	ccc	cgg
35	His	Phe	Ser	Thr	Ala	Pro	Pro	Asn	Pro	Asp	Ala	Pro	Trp	Thr	Pro	Arg
	576			180					185					190		
	gtg	gcc	ggc	ttt	aac	aag	cgc	gtc	ttc	tgc	gcc	gcg	gtc	ggg	cgc	ctg
40	Val	Ala	Gly	Phe	Asn	Lys	Arg	Val	Phe	Cys	Ala	Ala	Val	Gly	Arg	Leu
	624		195					200					205			
	gcg	gcc	atg	cat	gcc	cgg	atg	gcg	gct	gtc	cag	ctc	tgg	gac	atg	tcg
45	Ala	Ala	Met	His	Ala	Arg	Met	Ala	Ala	Val	Gln	Leu	Trp	Asp	Met	Ser
	672	210					215					220				
	cgt	ccg	cgc	aca	gac	gaa	gac	ctc	aac	gaa	ctc	ctt	ggc	atc	acc	acc
50	Arg	Pro	Arg	Thr	Asp	Glu	Asp	Leu	Asn	Glu	Leu	Leu	Gly	Ile	Thr	Thr
	720	225				230					235				240	
	atc	cgc	gtg	acg	gtc	tgc	gag	ggc	aaa	aac	ctg	ctt	cag	cgc	gcc	aac
55	Ile	Arg	Val	Thr	Val	Cys	Glu	Gly	Lys	Asn	Leu	Leu	Gln	Arg	Ala	Asn
	768				245					250					255	
	gag	ttg	gtg	aat	cca	gac	gtg	gtg	cag	gac	gtc	gac	gcg	gcc	acg	gcg
60	Glu	Leu	Val	Asn	Pro	Asp	Val	Val	Gln	Asp	Val	Asp	Ala	Ala	Thr	Ala
	816			260					265				270			
	act	cga	ggg	cgt	tct	gcg	gcg	tcg	cgc	ccc	acc	gag	cga	cct	cga	gcc
	864															

```

    Thr Arg Gly Arg Ser Ala Ala Ser Arg Pro Thr Glu Arg Pro Arg Ala
          275                280                285
5   cca gcc cgc tcc gct tct cgc ccc aga cgg ccc gtc gag ggt acc gag
    912
    Pro Ala Arg Ser Ala Ser Arg Pro Arg Arg Pro Val Glu Gly Thr Glu
      290                295                300
10  ctc gga tcc atg cat gga gat aca cct aca ttg cat gaa tat atg tta
    960
    Leu Gly Ser Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu
    305                310                315                320
15  gat ttg caa cca gag aca act gat ctc tac tgt tat gag caa tta aat
    1008
    Asp Leu Gln Pro Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn
          325                330                335
20  gac agc tca gag gag gag gat gaa ata gat ggt cca gct gga caa gca
    1056
    Asp Ser Ser Glu Glu Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala
          340                345                350
25  gaa ccg gac aga gcc cat tac aat att gta acc ttt tgt tgc aag tgt
    1104
    Glu Pro Asp Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys
          355                360                365
30  gac tct acg ctt cgg ttg tgc gta caa agc aca cac gta gac att cgt
    1152
    Asp Ser Thr Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg
          370                375                380
35  act ttg gaa gac ctg tta atg ggc aca cta gga att gtg tgc ccc atc
    1200
    Thr Leu Glu Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile
    385                390                395                400
40  tgt tct cag gat aag ctt aag ttt aaa ccg ctg atc agc ctc gac tgt
    1248
    Cys Ser Gln Asp Lys Leu Lys Phe Lys Pro Leu Ile Ser Leu Asp Cys
          405                410                415
45  gcc ttc tag
    1257
    Ala Phe

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The nucleic acid sequence of plasmid construct pcDNA3-ETA(dII)/E7 (SEQ ID
 NO: 4). ETA(dII)/E7 is ligated into the EcoRI/BamHI sites of pcDNA3 vector. The
 nucleotides encoding ETA(dII)/E7 are shown in upper case and underscored. Plasmid
 sequence is lower case.

Calreticulin (CRT)

Calreticulin (CRT), a well-characterized ~46 kDa protein was described briefly
 above, as were a number of its biological and biochemical activities. As used herein,
 “calreticulin” or “CRT” refers to polypeptides and nucleic acids molecules having

substantial identity to the exemplary human CRT sequences as described herein or homologues thereof, such as rabbit and rat CRT - well-known in the art. A CRT polypeptide is a polypeptide comprising a sequence identical to or substantially identical to the amino acid sequence of CRT. An exemplary nucleotide and amino acid sequence for a CRT used in the present compositions and methods are presented below. The terms “calreticulin” or “CRT” encompass native proteins as well as recombinantly produced modified proteins that, when fused with an antigen (at the DNA or protein level) promote the induction of immune responses and promote angiogenesis, including a CTL response. Thus, the terms “calreticulin” or “CRT” encompass homologues and allelic variants of human CRT, including variants of native proteins constructed by *in vitro* techniques, and proteins isolated from natural sources. The CRT polypeptides of the invention, and sequences encoding them, also include fusion proteins comprising non-CRT sequences, particularly MHC class I-binding peptides; and also further comprising other domains, *e.g.*, epitope tags, enzyme cleavage recognition sequences, signal sequences, secretion signals and the like.

A human CRT coding sequence is shown below (SEQ ID NO: 28):

```

1  atgtctgtat ccgtgccgt gctgctggc ctctcggcc tggccgtgc cgagcccgcc
61  gtctacttca aggagcagtt tctggacgga gacgggtgga ctcccgtg gatcgaatcc
121 aaacacaagt cagatttgg caaatcgtt ctacgtccg gcaagttcta cggtagacgag
181 gagaaagata aaggtttgca gacaagccag gatgcacgt tttatgctct gtcggccagt
241 ttcgagcctt tcagcaaca aggccagacg ctggtggtgc agttcacggt gaaacatgag
301 cagaacatcg actgtggggg cggctatgtg aagctgttct ctaatagttt ggaccagaca
361 gacatgcacg gagactcaga atacaacatc atgtttggc cgcacatctg tggccctggc
421 accaagaagg tcatgtcat ctcaactac aagggaaga acgtgctgat caacaaggac
481 atccgttgca aggatgatga gtttacacac ctgtacacac tgattgtgcg gccagacaac
541 acctatgagg tgaagattga caacagccag gtggagtccg gtccttgga agacgattgg
601 gacttcctgc caccaagaa gataaaggat cctgatgctt caaaaccgga agactgggat
661 gagcggggcca agatcgatga tcccacagac tccaagcctg aggactggga caagcccag
721 catatccctg accctgatgc taagaagccc gaggactggg atgaagagat ggacggagag
781 tgggaacccc cagtattca gaaccctgag tacaagggtg agtgaagcc ccggcagat
841 gacaaccag attacaaggg cacttgatc caccagaaa ttgacaacc cgagtattct
901 cccgatccca gtatctatgc ctatgataac ttggcgtgc tgggcctgga cctctggcag
961 gtcaagtctg gcaccatctt tgacaacttc ctatcacca acgatgaggc atacgctgag

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1021 gagtttggca acgagacgtg gggcgtaaca aaggcagcag agaaacaaat gaaggacaaa
 1081 caggacgagg agcagaggct taaggaggag gaagaagaca agaaacgcaa agaggaggag
 1141 gaggcagagg acaaggagga tgatgaggac aaagatgagg atgaggagga tgaggaggac
 1201 aaggaggaag atgaggagga agatgtcccc ggccaggcca aggacgagct *gtag* 1251

5 The amino acid sequence of the human CRT protein encoded by SEQ ID NO: 28 is set forth below (SEQ ID NO: 29). This amino acid sequence is highly homologous to GenBank Accession No. NM 004343.

1 MLLSVPLLLG LLGLAVAEPV VYFKEQFLDG DGWTSRWIES KHKSDFGKFF
 LSSGKFYGDV
 10 61 EKDKGLQTSQ DARFYALSAS FEPFSNKGQT LVVQFTVKHE QNIDCGGGYV
 KLFPNSLDQT
 121 DMHGDSEYNI MFGPDICGPG TTKVHVIFNY KGKNVLINKD IRCKDDEFTH
 LYTLIVRPDN
 181 TYEVKIDNSQ VESGSLEDDW DFLPPKKIKD PDASKPEDWD ERAKIDDPD
 15 SKPEDWDKPE
 241 HIPDPDAKKP EDWDEEMDGE WEPPVIQNPE YKGEWKPRQI DNPDYKGTWI
 HPEIDNPEYS
 301 PDPSIYAYDN FGVGLDLWQ VKSGTIFDNF LITNDEAYAE EFGNETWGV
 KAAEKQMKDK
 20 361 QDEEQRLKEE EEDKKRKEEE EAEDKEDDED KDEDEEDEED KEEDEEEDVP
 GQAKDEL 417

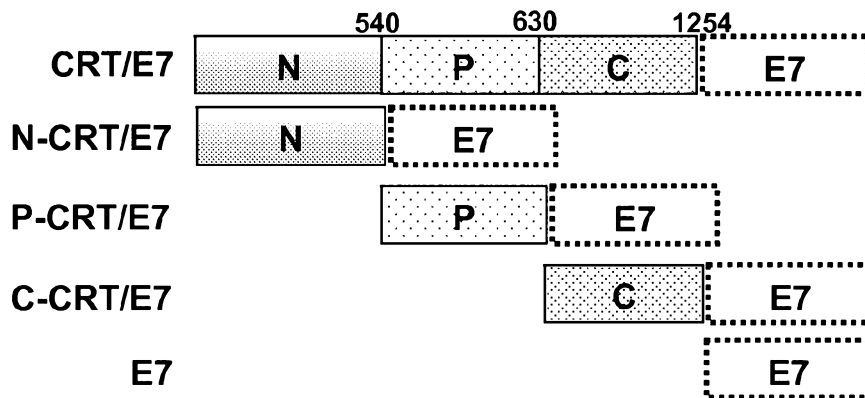
The amino acid sequence of the rabbit and rat CRT proteins are set forth in GenBank Accession Nos. P1553 and NM 022399, respectively. An alignment of human, rabbit and rat CRT shows that these proteins are highly conserved, and most of the amino
 25 acid differences between species are conservative in nature. Most of the variation is found in the alignment of the approximately 36 C-terminal residues. Thus, for the present invention, human CRT may be used as well as, DNA encoding any homologue of CRT from any species that has the requisite biological activity (as an IPP) or any active domain or fragment thereof, may be used in place of human CRT or a domain thereof.

30 The present inventors and colleagues (Cheng *et al.*, *supra*; incorporated by reference in its entirety) that DNA vaccines encoding each of the N, P, and C domains of CRT chimerically linked to HPV-16 E7 elicited potent antigen-specific CD8⁺ T cell responses and antitumor immunity in mice vaccinated i.d., by gene gun administration. N-

CRT/E7, P-CRT/E7 or C-CRT/E7 DNA each exhibited significantly increased numbers of E7-specific CD8⁺ T cell precursors and impressive antitumor effects against E7-expressing tumors when compared with mice vaccinated with E7 DNA (antigen only). N-CRT DNA administration also resulted in anti-angiogenic antitumor effects. Thus, cancer therapy

5 using DNA encoding N-CRT linked to a tumor antigen may be used for treating tumors through a combination of antigen-specific immunotherapy and inhibition of angiogenesis.

The constructs comprising CRT or one of its domains linked to E7 is illustrated schematically below.



10 The amino acid sequences of the 3 human CRT domains are shown as annotations of the full length protein (SEQ ID NO: 29). The N domain comprises residues 1-170 (normal text); the P domain comprises residues 171-269 (underscored); and the C domain comprises residues 270-417 (bold/italic)

1 MLLSVPLLLG LLGLAVAEPV VYFKEQFLDG DGWTSRWIES
 15 KHKSDFGKFV LSSGKFYGD
 61 EKDKGLQTSQ DARFYALSAS FEPFSNKGQT LVVQFTVKHE
 QNIDCGGGYV KLFPNSLDQT
 121 DMHGDSEYNI MFGPDICGPG TTKVHVIFNY KGKNVLINKD
 IRCKDDEFTH LYTLIVRPDN
 20 181 TYEVKIDNSQ VESGSLEDDW DFLPPKKIKD PDASKPEDWD
ERAKIDDPD SKPEDWDKPE
 241 HIPDPAKKP EDWDEEMDGE WEPPVIQNPE YKGEWKPRQI
DNPDYKGTWI HPEIDNPEYS
 301 ***PDPSIYAYDN FGVGLDLWQ VKSGTIFDNF LITNDEAYAE***
 25 ***EFGNETWGVT KAAEKQMKDK***

361 ***QDEEQRLKEE EEDKKRKEEE EAEDKEDDED KDEDEEDEED***
KEEDEEEDVP GQAKDEL 417

The sequences of the three domains are shown as separate polypeptides below:

Human N-CRT (SEQ ID NO: 30)

5 1 MLLSVPLLGLLGLAVAEPV VYFKEQFLDG DGWTSRWIES
 KHKSDFGKFFV LSSGKFFYGDE
 61 EKDKGLQTSQ DARFYALSAS FEPFSNKGQT LVVQFTVKHE
 QNIDCGGGYV KLFPNSLDQT
 121 DMHGDSEYNI MFGPDICGPG TTKVHVIFNY KGKNVLINKD
 10 IRCKDDEFTH **170**

Human P-CRT (SEQ ID NO: 31)

 1 LYTLIVRPDN TYEVKIDNSQ VESGSLEDDW DFLPPKKIKD
 PDASKPEDWD ERAKIDDPTD
 61 SKPEDWDKPE HIPDPDAKKP EDWDEEMDGE WEPPVIQNPE
 15 YKGEWKPRQ **109**

Human C-CRT (SEQ ID NO: 32)

 1 IDNPDYKGTW IHPEIDNPEY SPDPSIYAYD NFGVLGLDLW
 QVKSGTIFDN FLITNDEAYA
 61 EEFGNETWGV TKAAEKQMKD KQDEEQRLKE EEEDKKRKEE
 20 EEAEDKEDDE DKDEDEEDEE
 121 DKEEDEEEDV PGQAKDEL **138**

 The present vectors may comprises DNA encoding one or more of these domain
 sequences, which are shown by annotation of SEQ ID NO: 28, below, wherein the N-
 domain sequence is upper case, the P-domain sequence is lower case/italic/underscored,
 25 and the C domain sequence is lower case. The stop codon is also shown but not counted.

 1 **ATGCTGCTAT** CCGTGCCGCT GCTGCTCGGC CTCCTCGGCC
 TGGCCGTCGC CGAGCCCGCC
 61 GTCTACTTCA AGGAGCAGTT TCTGGACGGA GACGGGTGGA
 CTTCCCGCTG GATCGAATCC
 30 121 AAACACAAGT CAGATTTTGG CAAATTCGTT CTCAGTTCCG
 GCAAGTTCTA CGGTGACGAG
 181 GAGAAAGATA AAGGTTTGCA GACAAGCCAG GATGCACGCT
 TTTATGCTCT GTCGGCCAGT

241 TTCGAGCCTT TCAGCAACAA AGGCCAGACG CTGGTGGTGC
 AGTTCACGGT GAAACATGAG
 301 CAGAACATCG ACTGTGGGGG CGGCTATGTG AAGCTGTTTC
 CTAATAGTTT GGACCAGACA
 5 361 GACATGCACG GAGACTCAGA ATACAACATC ATGTTTGGTC
 CCGACATCTG TGGCCCTGGC
 421 ACCAAGAAGG TTCATGTCAT CTTCAACTAC AAGGGCAAGA
 ACGTGCTGAT CAACAAGGAC
 481 ATCCGTTGCA AGGATGATGA GTTTACACAC CTGTACACAC
 10 TGATTGTGCG GCCAGACAAC
541 acctatgagg tgaagattga caacagccag gtggagtccg gctccttgga agacgattgg
601 gacttcctgc caccaagaa gataaaggat cctgatgctt caaaaccgga agactgggat
661 gagcgggcca agatcgatga tcccacagac tccaagcctg aggactggga caagcccag
721 catatccctg accctgatgc taagaagccc gaggactggg atgaagagat ggacggagag
 15 781 tgggaacccc cagtattca gaaccctgag tacaagggtg agtggaaacc ccggcagatc
 841 gacaaccag attacaaggg cacttgatc caccagaaa ttgacaacc cgagtattct
 901 cccgatccca gtatctatgc ctatgataac ttggcgtgc tgggcctgga cctctggcag
 961 gtcaagtctg gcaccatctt tgacaacttc ctcacacca acgatgaggc atacgtgag
 1021 gagtttgcca acgagacgtg gggcgtaaca aaggcagcag agaacaat gaaggacaaa
 20 1081 caggacgagg agcagaggct taaggaggag gaagaagaca agaaacgcaa agaggaggag
 1141 gaggcagagg acaaggagga tgatgaggac aaagatgagg atgaggagga tgaggaggac
 1201 aaggaggaag atgaggagga agatgtcccc ggccaggcca aggacgagct gtag 1251

The coding sequence for each separate domain is provided below:

Human N-CRT DNA (SEQ ID NO: 33)

25 1 ATGCTGCTAT CCGTGCCGCT GCTGCTCGGC CTCCTCGGCC
 TGGCCGTCGC CGAGCCCGCC
 61 GTCTACTTCA AGGAGCAGTT TCTGGACGGA GACGGGTGGA
 CTTCCCGCTG GATCGAATCC
 121 AAACACAAGT CAGATTTTGG CAAATTCGTT CTCAGTTCCG
 30 GCAAGTTCTA CGGTGACGAG
 181 GAGAAAGATA AAGGTTTGCA GACAAGCCAG GATGCACGCT
 TTTATGCTCT GTCGGCCAGT

241 TTCGAGCCTT TCAGCAACAA AGGCCAGACG CTGGTGGTGC
 AGTTCACGGT GAAACATGAG
 301 CAGAACATCG ACTGTGGGGG CGGCTATGTG AAGCTGTTTC
 CTAATAGTTT GGACCAGACA
 5 361 GACATGCACG GAGACTCAGA ATACAACATC ATGTTTGGTC
 CCGACATCTG TGGCCCTGGC
 421 ACCAAGAAGG TTCATGTCAT CTTCAACTAC AAGGGCAAGA
 ACGTGCTGAT CAACAAGGAC
 481 ATCCGTTGCA AGGATGATGA GTTTACACAC CTGTACACAC
 10 TGATTGTGCG GCCAGACAAC

Human P-CRT DNA (SEQ ID NO: 34)

1 acctatgagg tgaagattga caacagccag gtggagtccg gctccttggga agacgattgg
 61 gacttcctgc cacccaagaa gataaaggat cctgatgctt caaaaccgga agactgggat
 121 gagcggggcca agatcgatga tcccacagac tccaagcctg aggactggga caagcccag
 15 181 catatccctg accctgatgc taagaagccc gaggactggg atgaagagat ggacggagag
 241 tgggaacccc cagtattca gaacct 267

Human C-CRT DNA (SEQ ID NO: 35)

1 gagtacaagg gtgagtggaa gccccggcag atcgacaacc cagattacaa gggcacttgg 61
 atccaccag aaattgacaa ccccgagat tctccgatc ccagtatcta tgctatgat 121 aactttggcg
 20 tgctgggcct ggacctctgg caggtaagt ctggcaccat ctttgacaac 181 ttctcatca ccaacgatga
 ggcatagct gaggagtgtg gcaacgagac gtggggcgta 241 acaaaggcag cagagaaaca
 aatgaaggac aaacaggacg aggagcagag gcttaaggag 301 gaggaagaag acaagaacg
 caaaggagg gaggaggcag aggacaagga ggatgatgag 361 gacaaagatg aggatgagga
 ggatgaggag gacaaggagg aagatgagga ggaagatgtc 421 cccggccagg ccaaggacga gctg
 25 444

Alternatively, any nucleotide sequences that encodes these domains may be used in the present constructs. Thus, for use in humans, the sequences may be further codon-optimized.

The present construct may employ combinations of one or more CRT domains, in
 30 any of a number of orientations. Using the designations N^{CRT} , P^{CRT} and C^{CRT} to designate the domains, the following are but a few examples of the combinations that may be used in the DNA vaccine vectors of the present invention (where it is understood that **Ag** can be any antigen, including E7(detox) or E6 (detox).

$N^{CRT} - P^{CRT} - Ag;$ $N^{CRT} - P^{CRT} - Ag;$ $N^{CRT} - C^{CRT} - Ag;$ $N^{CRT} - N^{CRT} - Ag;$
 $N^{CRT} - N^{CRT} - N^{CRT} - Ag;$ $P^{CRT} - P^{CRT} - Ag;$ $P^{CRT} - C^{CRT} - Ag;$ $P^{CRT} - N^{CRT} - Ag;$
 $C^{CRT} - P^{CRT} - Ag;$ $N^{CRT} - P^{CRT} - Ag;$ *etc.*

The present invention may employ shorter polypeptide fragments of CRT or CRT domains provided such fragments can enhance the immune response to an antigen with which they are paired. Shorter peptides from the CRT or domain sequences shown above that have the ability to promote protein processing via the MHC-1 class I pathway are also
 5 included, and may be defined by routine experimentation.

The present invention may also employ shorter nucleic acid fragments that encode CRT or CRT domains provided such fragments are functional, *e.g.*, encode polypeptides that can enhance the immune response to an antigen with which they are paired (*e.g.*, linked). Nucleic acids that encode shorter peptides from the CRT or domain sequences
 10 shown above and are functional, *e.g.*, have the ability to promote protein processing via the MHC-1 class I pathway, are also included, and may be defined by routine experimentation.

A polypeptide fragment of CRT may include at least or about 50, 100, 200, 300, or 400 amino acids. A polypeptide fragment of CRT may also include at least or about 25, 50, 75, 100, 25-50, 50-100, or 75-125 amino acids from a CRT domain selected from the group
 15 N-CRT, P-CRT, and C-CRT. A polypeptide fragment of CRT may include residues 1-50, 50-75, 75-100, 100-125, 125-150, 150-170 of the N-domain (*e.g.*, of SEQ ID NO: 30). A polypeptide fragment of CRT may include residues 1-50, 50-75, 75-100, 100-109 of the P-domain (*e.g.*, of SEQ ID NO: 31). A polypeptide fragment of CRT may include residues 1-50, 50-75, 75-100, 100-125, 125-138 of the C-domain (*e.g.*, of SEQ ID NO: 32).

20 A nucleic acid fragment of CRT may encode at least or about 50, 100, 200, 300, or 400 amino acids. A nucleic acid fragment of CRT may also encode at least or about 25, 50, 75, 100, 25-50, 50-100, or 75-125 amino acids from a CRT domain selected from the group N-CRT, P-CRT, and C-CRT. A nucleic acid fragment of CRT may encode residues 1-50, 50-75, 75-100, 100-125, 125-150, 150-170 of the N-domain (*e.g.*, of SEQ ID NO: 30). A
 25 nucleic acid fragment of CRT may encode residues 1-50, 50-75, 75-100, 100-109 of the P-domain (*e.g.*, of SEQ ID NO: 31). A nucleic acid fragment of CRT may encode residues 1-50, 50-75, 75-100, 100-125, 125-138 of the C-domain (*e.g.*, of SEQ ID NO: 32).

Polypeptide "fragments" of CRT, as provided herein, do not include full-length CRT. Likewise, nucleic acid "fragments" of CRT, as provided herein, do not include a full-
 30 length CRT nucleic acid sequence and do not encode a full-length CRT polypeptide.

In one embodiment, a vector construct of a complete chimeric nucleic acid of the invention, is shown below (SEQ ID NO: 36). The sequence is annotated to show plasmid-derived nucleotides (lower case letters), CRT-derived nucleotides (upper case bold letters), and HPV-E7-derived nucleotides (upper case, italicized/underlined letters). Note that 5 plasmid nucleotides are found between the CRT and E7 coding sequences and that the stop codon for the E7 sequence is double underscored. This plasmid is also referred to as pNGVL4a-CRT/E7(detox).

```

1   gctccgcccc cctgacgagc atcacaaaaa tcgacgctca agtcagaggt ggcgaaaccc
61  gagaggacta taaagatacc aggcgtttcc ccctggaagc tcctcgtgc gctctcgtg
10  121 tccgacctg ccgcttaccg gatacctgc cgcctttctc ccttcgggaa gcgtggcgct
181 ttctcatagc tcacgctgta ggtatctcag ttcggtgtag gtcgttcgct ccaagctggg
241 ctgtgtgcac gaaccccccg ttcagcccgga ccgctgcgcc ttatccggtg actatcgtct
301 tgagtccaac ccggttaagac acgacttata gccactggca gcagccactg gtaacaggat
361 tagcagagcg aggtatgtag gcggtgctac agagtcttg aagtgggtgc ctaactacgg
15  421 ctacactaga agaacagtat ttggtatctg cgctctgctg aagccagtta ccttcggaaa
481 aagagttggt agctcttgat ccggcaaaaa aaccaccgct ggtagcggtg gttttttgt
541 ttgcaagcag cagattacgc gcagaaaaaa aggatctcaa gaagatcctt tgatctttc
601 tacgggggtct gacgctcagt ggaacgaaaa ctacagttaa gggattttgg tcatgagatt
661 atcaaaaagg atcttcacct agatcctttt aaattaaaaa tgaagtttta aatcaatcta
20  721 aagtatatat gagtaaactt ggtctgacag ttaccaatgc ttaatcagtg aggcacctat
781 ctacgcgata tgtctatttc gttcatccat agttgcctga ctcggggggg gggggcgctg
841 aggtctgcct cgtgaagaag gtgttgctga ctataccag ggcaacgttg ttgccattgc
901 tacaggcatc gtggtgtcac gctcgtcgtt tggatggct tcattcagct ccggttccca
961 acgatcaagg cgagttacat gatcccccat gttgtgcaaa aaagcgggta gtccttcgg
25  1021 tctccgatac gttgtcagaa gtaagttggc cgcagtggtt tcatctatgg ttatggcagc
1081 actgcataat tccttactg tcatgccatc cgtaagatgc tttctgtga ctggtgagta
1141 ctcaaccaag tcattctgag aatagtgtat gcggcgaccg agttgctctt gcccggcgtc
1201 aatacgggat aataccgcgc cacatagcag aactttaaaa gtgctcatca ttggaaaacg
1261 ttcttcgggg cgaaaactct caaggatctt accgctgttg agatccagtt cgatgtaacc
30  1321 cactcgtgca cctgaatcgc cccatcatcc agccagaaaag tgagggagcc acggttgatg
1381 agagctttgt ttaggtgga ccagttggtg atttgaact tttgctttgc cacggaacgg
1441 tctgcgttgt cggaagatg cgtgatctga tcttcaact cagcaaaaagt tcgatttatt
1501 caacaaagcc gccgtcccg caagtcagcg taatgctctg ccagtgttac aaccaattaa

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1561 ccaattctga ttagaaaaac tcacgagca tcaaatgaaa ctgcaattta ttcatatcag
 1621 gattatcaat accatatttt tgaaaaagcc gtttctgtaa tgaaggagaa aactcaccga
 1681 ggcagttcca taggatggca agatcctggg atcggctcgc gattccgact cgtccaacat
 1741 caatacaacc tattaatttc cctcgtcaa aaataagggt atcaagttag aaatcaccat
 5 1801 gagtgacgac tgaatccggt gagaatggca aaagcttatg catttcttc cagacttggt
 1861 caacaggcca gccattacgc tcgtcatcaa aatcactcgc atcaacaaa ccgttattca
 1921 ttcgtgattg cgcctgagcg agacgaaata cgcgatcgtc gttaaaggga caattacaaa
 1981 caggaatcga atgcaaccgg cgcaggaaca ctgccagcgc atcaacaata tttcacctg
 2041 aatcaggata ttcttcta atctggaatg ctgtttccc ggggatcgcg gtggtgagta
 10 2101 accatgcac atcaggagta cggataaaat gcttgatggt cggaagaggc ataaattccg
 2161 tcagccagtt tagtctgacc atctcatctg taacatcatt ggcaacgcta cctttgccat
 2221 gtttcagaaa caactctggc gcacgggct tccatacaa tcgatatgatt gtcgcacctg
 2281 attgcccgc attatcgcga gcccatatat accatataa atcagcatcc atgttggaat
 2341 ttaatcgcg cctcgagcaa gacgtttccc gttgaatatg gtcataaca ccccttgat
 15 2401 tactgtttat gtaagcagac agttttattg ttcattgatg tatatttta tctgtgcaa
 2461 tgtaacatca gagattttga gacacaacgt ggctttcccc cccccccat tattgaagca
 2521 tttatcaggg ttattgtctc atgagcggat acataattga atgtatttag aaaaataaac
 2581 aaataggggt tccgcgcaca tttccccgaa aagtgccacc tgacgtctaa gaaaccatta
 2641 ttatcatgac attaacctat aaaaataggc gtatcacgag gcccttctgt ctgcgcggt
 20 2701 tcggtgatga cggtgaaaac ctctgacaca tgcagctccc ggagacggtc acagcttgtc
 2761 tgtaagcgga tgccgggagc agacaagccc gtcagggcgc gtcagcgggt gttggcgggt
 2821 gtcggggctg gcttaactat gcggcatcag agcagattgt actgagagtg caccatatgc
 2881 ggtgtgaaat accgcacaga tgcgtaagga gaaaataccg catcagattg gctattggcc
 2941 attgcatacg ttgtatccat atcataatat gtacatttat attggctcat gtccaacatt
 25 3001 accgcatgt tgacattgat tattgactag ttattaatag taatcaatta cggggctcatt
 3061 agttcatagc ccatatatgg agttccgctg tacataactt acggtaaatg gcccgcctgg
 3121 ctgaccgccc aacgaccccc gccattgac gtcaataatg acgtatgttc ccatagtaac
 3181 gccaataggg actttccatt gacgtcaatg ggtggagtat ttacggtaaa ctgcccactt
 3241 ggcagtacat caagtgtatc atatgccaag tacgccccct attgacgtca atgacggtaa
 30 3301 atggcccggc tggcattatg ccagtagat gaccttatgg gactttccta cttggcagta
 3361 catctacgta ttagtcacg ctattaccat ggtgatgcgg ttttggcagt acatcaatgg
 3421 gcgtggatag cggtttgact cacgggggatt tccaagtctc caccctattg acgtcaatgg
 3481 gagtttgttt tggcacaaa atcaacggga ctttcaaaa tgcgtaaca actccgcccc

3541 attgacgcaa atgggcggta ggcgtgtacg gtgggaggtc tatataagca gagctcggtt
3601 agtgaaccgt cagatcgctt ggagacgcca tccacgtgt tttacctcc atagaagaca
3661 ccgggaccga tccagcctcc gcggccggga acggtgcatt ggaacgcgga tccccgtgc
3721 caagagtac gtaagtaccg cctatagact ctataggcac acccctttgg ctcttatgca
5 3781 tgctatactg ttttggctt ggggcctata cccccgct tcctatgct ataggtgatg
3841 gtatagctta gcctataggt gtgggttatt gaccattatt gaccactcca acggtggagg
3901 gcagtgtagt ctgagcagta ctcgtgtcg ccgcgcgcgc caccagacat aatagctgac
3961 agactaacag actgttctt tccatgggtc ttttctgcag tcaccgtcgt cgac**ATGCTG**
4021 CTATCCGTGC CGCTGCTGCT CGGCCTCCTC GGCCTGGCCG
10 **TCGCCGAGCC TGCCGTCTAC**
4081 TTCAAGGAGC AGTTTCTGGA CGGGGACGGG TGGACTTCCC
GCTGGATCGA ATCCAAACAC
4141 AAGTCAGATT TTGGCAAATT CGTTCTCAGT TCCGGCAAGT
TCTACGGTGA CGAGGAGAAA
15 **4201 GATAAAGGTT TGCAGACAAG CCAGGATGCA CGCTTTTATG**
CTCTGTCCGC CAGTTTCGAG
4261 CCTTTCAGCA ACAAAGGCCA GACGCTGGTG GTGCAGTTCA
CGGTGAAACA TGAGCAGAAC
4321 ATCGACTGTG GGGGCGGCTA TGTGAAGCTG TTTCCTAATA
20 **GTTTGGACCA GACAGACATG**
4381 CACGGAGACT CAGAATACAA CATCATGTTT GGTCCCGACA
TCTGTGGCCC TGGCACCAAG
4441 AAGGTTTCATG TCATCTTCAA CTACAAGGGC AAGAACGTGC
TGATCAACAA GGACATCCGT
25 **4501 TGCAAGGATG ATGAGTTTAC ACACCTGTAC AACTGATTG**
TGCGGCCAGA CAACACCTAT
4561 GAGGTGAAGA TTGACAACAG CCAGGTGGAG TCCGGCTCCT
TGGAAGACGA TTGGGACTTC
4621 CTGCCACCCA AGAAGATAAA GGATCCTGAT GCTTCAAAC
30 **CGGAAGACTG GGATGAGCGG**
4681 GCCAAGATCG ATGATCCCAC AGACTCCAAG CCTGAGGACT
GGGACAAGCC CGAGCATATC

- 4741 CCTGACCCTG ATGCTAAGAA GCCCGAGGAC TGGGATGAAG
AGATGGACGG AGAGTGGGAA
- 4801 CCCCCAGTGA TTCAGAACCC TGAGTACAAG GGTGAGTGGA
AGCCCCGGCA GATCGACAAC
- 5 4861 CCAGATTACA AGGGCACTTG GATCCACCCA GAAATTGACA
ACCCCGAGTA TTCTCCCGAT
- 4921 CCCAGTATCT ATGCCTATGA TAACTTTGGC GTGCTGGGCC
TGGACCTCTG GCAGGTCAAG
- 4981 TCTGGCACCA TCTTTGACAA CTTCTCATC ACCAACGATG
- 10 AGGCATACGC TGAGGAGTTT
- 5041 GGCAACGAGA CGTGGGGCGT AACAAAGGCA GCAGAGAAAC
AAATGAAGGA CAAACAGGAC
- 5101 GAGGAGCAGA GGCTTAAGGA GGAGGAAGAA GACAAGAAAC
GCAAAGAGGA GGAGGAGGCA
- 15 5161 GAGGACAAGG AGGATGATGA GGACAAAGAT GAGGATGAGG
AGGATGAGGA GGACAAGGAG
- 5221 GAAGATGAGG AGGAAGATGT CCCC GGCCAG GCCAAGGACG
AGCTGgaatt CATGCATGGA
- 5281 GATACACCTA CATTGCATGA ATATATGTTA GATTGCAAC CAGAGACAAC
- 20 TGATCTCTAC
- 5341 GGTATGGGC AATTAAATGA CAGCTCAGAG GAGGAGGATG
AAATAGATGG TCCAGCTGGA
- 5401 CAAGCAGAAC CGGACAGAGC CCATTACAAT ATTGTAACCT TTTGTTGCAA
GTGTGACTCT
- 25 5461 ACGCTTCGGT TGTGCGTACA AAGCACACAC GTAGACATTC GTACTTTGGA
AGACCTGTTA
- 5521 ATGGGCACAC TAGGAATTGT GTGCCCCATC TGTTCTCAGA AACCATAAagg
atccagatct
- 5581 tttccctct gccaaaaatt atggggacat catgaagccc cttgagcctc tgacttctgg
- 30 5641 ctaataaagg aaatttattt tcattgcaat agtgtgttgg aattttttgt gtctctcact
- 5701 cggaaggaca tatgggaggg caaatcattt aaaacatcag aatgagtatt tggtttagag
- 5761 tttggcaaca tatgcccaatt cttccgcttc ctcgctcact gactcgtgc gctcggctgt
- 5821 tcggctgcgg cgagcgggtat cagctcactc aaaggcggta atacggttat ccacagaatc

5881 aggggataac gcaggaaaga acatgtgagc aaaaggccag caaaaggcca ggaaccgtaa
 5941 aaaggccgcg ttgctggcgt tttccatag **5970**

The Table below describes the structure of the above plasmid.

Plasmid Position	Genetic Construct	Source of Construct
5970-0823	E. coli ORI (ColEI)	pBR / <i>E. coli</i> -derived
0837-0881	portion of transposase (tpnA)	Common plasmid sequence Tn5/Tn903
0882-1332	β -Lactamase (Amp ^R)	pBRpUC derived plasmid
1331-2496	AphA (Kan ^R)	Tn903
2509-2691	P3 Promoter DNA binding site	Tn3/pBR322
2692-2926	pUC backbone	Common plasmid sequence pBR322-derived
2931-4009	NF1 binding and promoter	HHV-5(HCMV UL-10 IE1 gene)
4010-4014	Poly-cloning site	Common plasmid sequence
4015 - 5265	Calreticulin (CRT)	Human Calreticulin
5266-5271	GAATTC plasmid sequence	Remain after cloning
5272-5568	dE7 gene (detoxified partial)	HPV-16 (E7 gene) incl. stop codon
5569-5580	Poly-cloning site	Common plasmid sequence
551-5970	Poly-Adenylation site	Mammalian signal, pHCMV-derived

5

In some embodiments, an alternative to CRT is another ER chaperone polypeptide exemplified by ER60, GRP94 or gp96, well-characterized ER chaperone polypeptide that representatives of the HSP90 family of stress-induced proteins (see WO 02/012281, incorporated herein by reference). The term “endoplasmic reticulum chaperone polypeptide” as used herein means any polypeptide having substantially the same ER chaperone function as the exemplary chaperone proteins CRT, tapasin, ER60 or calnexin. Thus, the term includes all functional fragments or variants or mimics thereof. A polypeptide or peptide can be routinely screened for its activity as an ER chaperone using assays known in the art. While the invention is not limited by any particular mechanism of action, *in vivo* chaperones promote the correct folding and oligomerization of many

10

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glycoproteins in the ER, including the assembly of the MHC class I heterotrimeric molecule (heavy (H) chain, β_2m , and peptide). They also retain incompletely assembled MHC class I heterotrimeric complexes in the ER (Hauri FEBS Lett. 476:32-37, 2000).

5 *Intercellular spreading proteins*

The potency of naked DNA vaccines may be enhanced by their ability to amplify and spread *in vivo*. VP22, a herpes simplex virus type 1 (HSV-1) protein and its "homologues" in other herpes viruses, such as the avian Marek's Disease Virus (MDV) have the property of intercellular transport that provide an approach for enhancing vaccine
10 potency. The present inventors have previously created novel fusions of VP22 with a model antigen, human papillomavirus type 16 (HPV-16) E7, in a DNA vaccine which generated enhanced spreading and MHC class I presentation of antigen. These properties led to a dramatic increase in the number of E7-specific CD8⁺ T cell precursors in vaccinated mice (at least 50-fold) and converted a less effective DNA vaccine into one with
15 significant potency against E7-expressing tumors. In comparison, a non-spreading mutant, VP22(1-267), failed to enhance vaccine potency. Results presented in U.S. Patent Application publication No. 20040028693 (US Patent No. 7,318,928), hereby incorporated by reference in its entirety, show that the potency of DNA vaccines is dramatically improved through enhanced intercellular spreading and MHC class I presentation of the
20 antigen.

A similar study linking MDV-1 UL49 to E7 also led to a dramatic increase in the number of E7-specific CD8⁺ T cell precursors and potency response against E7-expressing tumors in vaccinated mice. Mice vaccinated with a MDV-1 UL49 DNA vaccine stimulated E7-specific CD8⁺ T cell precursor at a level comparable to that induced by HSV-1
25 VP22/E7. Thus, fusion of MDV-1UL49 DNA to DNA encoding a target antigen gene significantly enhances the DNA vaccine potency.

In one embodiment, the spreading protein may be a viral spreading protein, including a herpes virus VP22 protein. Exemplified herein are fusion constructs that comprise herpes simplex virus-1 (HSV-1) VP22 (abbreviated HVP22) and its homologue
30 from Marek's disease virus (MDV) termed MDV-VP22 or MVP-22. Also included in the invention are homologues of VP22 from other members of the herpesviridae or polypeptides from nonviral sources that are considered to be homologous and share the functional characteristic of promoting intercellular spreading of a polypeptide or peptide

that is fused or chemically conjugated thereto.

DNA encoding HVP22 has the sequence SEQ ID NO: 7 as nucleotides 1-921 of the longer sequence SEQ ID NO: 6 (which is the full length nucleotide sequence of a vector that comprises HVP22). DNA encoding MDV-VP22 is SEQ ID NO: 37 shown below:

```

5  1 atg ggg gat tct gaa agg cgg aaa tcg gaa cgg cgt cgt tcc ctt gga 48 tat ccc tct gca tat gat gac
   gtc tcg att cct gct cgc aga cca tca 96 aca cgt act cag cga aat tta aac cag gat gat ttg tca aaa cat
   gga 144 cca ttt acc gac cat cca aca caa aaa cat aaa tcg gcg aaa gcc gta 192 tcg gaa gac gtt
   tcg tct acc acc cgg ggt ggc ttt aca aac aaa ccc 240 cgt acc aag ccc ggg gtc aga gct gta caa
   agt aat aaa ttc gct ttc 288 agt acg gct cct tca tca gca tct agc act tgg aga tca aat aca gtg 336
10 gca ttt aat cag cgt atg ttt tgc gga gcg gtt gca act gtg gct caa 384 tat cac gca tac caa ggc gcg
   ctc gcc ctt tgg cgt caa gat cct ccg 432 cga aca aat gaa gaa tta gat gca ttt ctt tcc aga gct gtc att
   aaa 480 att acc att caa gag ggt cca aat ttg atg ggg gaa gcc gaa acc tgt 528 gcc cgc aaa cta ttg
   gaa gag tct gga tta tcc cag ggg aac gag aac 576 gta aag tcc aaa tot gaa cgt aca acc aaa tct
   gaa cgt aca aga cgc 624 ggc ggt gaa att gaa atc aaa tcg cca gat ccg gga tct cat cgt aca 672
15 cat aac cct cgc act ccc gca act tcg cgt cgc cat cat tca tcc gcc 720 cgc gga tat cgt agc agt gat
   agc gaa taa 747

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The amino acid sequence of HVP22 polypeptide is SEQ ID NO: 38 as amino acid residues 1-301 of SEQ ID NO: 39 (the full length amino acid encoded by the vector).

The amino acid sequence of the MDV-VP22, SEQ ID NO: 40, is below:

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20  2 Met Gly Asp Ser Glu Arg Arg Lys Ser Glu Arg Arg Arg Ser Leu Gly 16 Tyr Pro Ser Ala
   Tyr Asp Asp Val Ser Ile Pro Ala Arg Arg Pro Ser 32 Thr Arg Thr Gln Arg Asn Leu Asn Gln
   Asp Asp Leu Ser Lys His Gly 48 Pro Phe Thr Asp His Pro Thr Gln Lys His Lys Ser Ala Lys
   Ala Val 64 Ser Glu Asp Val Ser Ser Thr Thr Arg Gly Gly Phe Thr Asn Lys Pro 80 Arg Thr
   Lys Pro Gly Val Arg Ala Val Gln Ser Asn Lys Phe Ala Phe 96 Ser Thr Ala Pro Ser Ser Ala
25  Ser Ser Thr Trp Arg Ser Asn Thr Val 112 Ala Phe Asn Gln Arg Met Phe Cys Gly Ala Val
   Ala Thr Val Ala Gln 128 Tyr His Ala Tyr Gln Gly Ala Leu Ala Leu Trp Arg Gln Asp Pro
   Pro 144 Arg Thr Asn Glu Glu Leu Asp Ala Phe Leu Ser Arg Ala Val Ile Lys 160 Ile Thr Ile
   Gln Glu Gly Pro Asn Leu Met Gly Glu Ala Glu Thr Cys 176 Ala Arg Lys Leu Leu Glu Glu
   Ser Gly Leu Ser Gln Gly Asn Glu Asn 192 Val Lys Ser Lys Ser Glu Arg Thr Thr Lys Ser
30  Glu Arg Thr Arg Arg 208 Gly Gly Glu Ile Glu Ile Lys Ser Pro Asp Pro Gly Ser His Arg Thr
   224 His Asn Pro Arg Thr Pro Ala Thr Ser Arg Arg His His Ser Ser Ala 240 Arg Gly Tyr Arg
   Ser Ser Asp Ser Glu -- 249

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A DNA clone pcDNA3 VP22/E7, that includes the coding sequence for HVP22 and

the HPV-16 protein, E7 (plus some additional vector sequence) is SEQ ID NO: 6.

The amino acid sequence of E7 (SEQ ID NO: 41) is residues 308-403 of SEQ ID NO: 39. This particular clone has only 96 of the 98 residues present in E7. The C-terminal residues of wild-type E7, Lys and Pro, are absent from this construct. This is an example of a deletion variant as the term is described below. Such deletion variants (*e.g.*, terminal truncation of two or a small number of amino acids) of other antigenic polypeptides are examples of the embodiments intended within the scope of the fusion polypeptides of this invention.

10 *Homologues of IPPs*

Homologues or variants of IPPs described herein, may also be used, provided that they have the requisite biological activity. These include various substitutions, deletions, or additions of the amino acid or nucleic acid sequences. Due to code degeneracy, for example, there may be considerable variation in nucleotide sequences encoding the same amino acid sequence.

A functional derivative of an IPP retains measurable IPP-like activity, including that of promoting immunogenicity of one or more antigenic epitopes fused thereto by promoting presentation by class I pathways. "Functional derivatives" encompass "variants" and "fragments" regardless of whether the terms are used in the conjunctive or the alternative herein.

The term "chimeric" or "fusion" polypeptide or protein refers to a composition comprising at least one polypeptide or peptide sequence or domain that is chemically bound in a linear fashion with a second polypeptide or peptide domain. One embodiment of this invention is an isolated or recombinant nucleic acid molecule encoding a fusion protein comprising at least two domains, wherein the first domain comprises an IPP and the second domain comprises an antigenic epitope, *e.g.*, an MHC class I-binding peptide epitope. The "fusion" can be an association generated by a peptide bond, a chemical linking, a charge interaction (*e.g.*, electrostatic attractions, such as salt bridges, H-bonding, *etc.*) or the like. If the polypeptides are recombinant, the "fusion protein" can be translated from a common mRNA. Alternatively, the compositions of the domains can be linked by any chemical or electrostatic means. The chimeric molecules of the invention (*e.g.*, targeting polypeptide fusion proteins) can also include additional sequences, *e.g.*, linkers, epitope tags, enzyme cleavage recognition sequences, signal sequences, secretion signals, and the like.

Alternatively, a peptide can be linked to a carrier simply to facilitate manipulation or identification/ location of the peptide.

Also included is a “functional derivative” of an IPP, which refers to an amino acid substitution variant, a “fragment” of the protein. A functional derivative of an IPP retains measurable activity that may be manifested as promoting immunogenicity of one or more antigenic epitopes fused thereto or co-administered therewith. “Functional derivatives” encompass “variants” and “fragments” regardless of whether the terms are used in the conjunctive or the alternative herein.

A functional homologue must possess the above biochemical and biological activity. In view of this functional characterization, use of homologous proteins including proteins not yet discovered, fall within the scope of the invention if these proteins have sequence similarity and the recited biochemical and biological activity.

To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In one embodiment, the method of alignment includes alignment of Cys residues.

In one embodiment, the length of a sequence being compared is at least 30%, at least 40%, at least 50%, at least 60%, and at least 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% of the length of the IPP reference sequence. The amino acid residues (or nucleotides) at corresponding amino acid (or nucleotide) positions are then compared. When a position in the first sequence is occupied by the same amino acid residue (or nucleotide) as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid “identity” is equivalent to amino acid or nucleic acid “homology”). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In one embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the

GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases, for example, to identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to IPP nucleic acid molecules. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to IPP protein molecules. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

Thus, a homologue of an IPP or of an IPP domain described above is characterized as having (a) functional activity of native IPP or domain thereof and (b) amino acid sequence similarity to a native IPP protein or domain thereof when determined as above, of at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

It is within the skill in the art to obtain and express such a protein using DNA probes based on the disclosed sequences of an IPP. Then, the fusion protein's biochemical and biological activity can be tested readily using art-recognized methods such as those described herein, for example, a T cell proliferation, cytokine secretion or a cytolytic assay, or an *in vivo* assay of tumor protection or tumor therapy. A biological assay of the

stimulation of antigen-specific T cell reactivity will indicate whether the homologue has the requisite activity to qualify as a “functional” homologue.

A “variant” refers to a molecule substantially identical to either the full protein or to a fragment thereof in which one or more amino acid residues have been replaced
 5 (substitution variant) or which has one or several residues deleted (deletion variant) or added (addition variant). A “fragment” of an IPP refers to any subset of the molecule, that is, a shorter polypeptide of the full-length protein.

A number of processes can be used to generate fragments, mutants and variants of the isolated DNA sequence. Small subregions or fragments of the nucleic acid encoding the
 10 spreading protein, for example 1-30 bases in length, can be prepared by standard, chemical synthesis. Antisense oligonucleotides and primers for use in the generation of larger synthetic fragment.

A one group of variants are those in which at least one amino acid residue and in certain embodiments only one, has been substituted by different residue. For a detailed
 15 description of protein chemistry and structure, see Schulz, GE *et al.*, *Principles of Protein Structure*, Springer-Verlag, New York, 1978, and Creighton, T.E., *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, 1983, which are hereby incorporated by reference. The types of substitutions that may be made in the protein molecule may be based on analysis of the frequencies of amino acid changes between a
 20 homologous protein of different species, such as those presented in Table 1-2 of Schulz *et al.* (*supra*) and Figure 3-9 of Creighton (*supra*). Based on such an analysis, conservative substitutions are defined herein as exchanges within one of the following five groups:

1. Small aliphatic, nonpolar or slightly polar residues Ala, Ser, Thr (Pro, Gly);
2. Polar, negatively charged residues and their amides Asp, Asn, Glu, Gln;
3. Polar, positively charged residues His, Arg, Lys;
4. Large aliphatic, nonpolar residues Met, Leu, Ile, Val (Cys)
5. Large aromatic residues Phe, Tyr, Trp.

The three amino acid residues in parentheses above have special roles in protein architecture. Gly is the only residue lacking a side chain and thus imparts flexibility to the
 25 chain. Pro, because of its unusual geometry, tightly constrains the chain. Cys can participate in disulfide bond formation, which is important in protein folding.

More substantial changes in biochemical, functional (or immunological) properties are made by selecting substitutions that are less conservative, such as between, rather than

within, the above five groups. Such changes will differ more significantly in their effect on maintaining (a) the structure of the peptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Examples of such substitutions are (i) substitution of Gly and/or Pro by another amino acid or deletion or insertion of Gly or Pro; (ii) substitution of a hydrophilic residue, *e.g.*, Ser or Thr, for (or by) a hydrophobic residue, *e.g.*, Leu, Ile, Phe, Val or Ala; (iii) substitution of a Cys residue for (or by) any other residue; (iv) substitution of a residue having an electropositive side chain, *e.g.*, Lys, Arg or His, for (or by) a residue having an electronegative charge, *e.g.*, Glu or Asp; or (v) substitution of a residue having a bulky side chain, *e.g.*, Phe, for (or by) a residue not having such a side chain, *e.g.*, Gly.

Most acceptable deletions, insertions and substitutions according to the present invention are those that do not produce radical changes in the characteristics of the wild-type or native protein in terms of its relevant biological activity, *e.g.*, its ability to stimulate antigen specific T cell reactivity to an antigenic epitope or epitopes that are fused to the protein. However, when it is difficult to predict the exact effect of the substitution, deletion or insertion in advance of doing so, one skilled in the art will appreciate that the effect can be evaluated by routine screening assays such as those described here, without requiring undue experimentation.

Exemplary fusion proteins provided herein comprise an IPP protein or homolog thereof and an antigen. For example, a fusion protein may comprise, consist essentially of, or consist of an IPP or an IPP fragment, *e.g.*, N-CRT, P-CRT and/or C-CRT, or an amino acid sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence of the IPP or IPP fragment, wherein the IPP fragment is functionally active as further described herein, linked to an antigen. A fusion protein may also comprise an IPP or an IPP fragment and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids, or about 1-5, 1-10, 1-15, 1-20, 1-25, 1-30, 1-50 amino acids, at the N- and/or C-terminus of the IPP fragment. These additional amino acids may have an amino acid sequence that is unrelated to the amino acid sequence at the corresponding position in the IPP protein.

Homologs of an IPP or an IPP fragments may also comprise, consist essentially of, or consist of an amino acid sequence that differs from that of an IPP or IPP fragment by the addition, deletion, or substitution, *e.g.*, conservative substitution, of at least about 1, 2, 3, 4,

5, 6, 7, 8, 9 or 10 amino acids, or from about 1-5, 1-10, 1-15 or 1-20 amino acids.

Homologs of an IPP or IPP fragments may be encoded by nucleotide sequences that are at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleotide sequence encoding an IPP or IPP fragment, such as those described herein.

Yet other homologs of an IPP or IPP fragments are encoded by nucleic acids that hybridize under stringent hybridization conditions to a nucleic acid that encodes an IPP or IPP fragment. For example, homologs may be encoded by nucleic acids that hybridize under high stringency conditions of 0.2 to 1 x SSC at 65 °C followed by a wash at 0.2 x SSC at 65 °C to a nucleic acid consisting of a sequence described herein. Nucleic acids that hybridize under low stringency conditions of 6 x SSC at room temperature followed by a wash at 2 x SSC at room temperature to nucleic acid consisting of a sequence described herein or a portion thereof can be used. Other hybridization conditions include 3 x SSC at 40 or 50 °C, followed by a wash in 1 or 2 x SSC at 20, 30, 40, 50, 60, or 65 °C.

Hybridizations can be conducted in the presence of formaldehyde, *e.g.*, 10%, 20%, 30% 40% or 50%, which further increases the stringency of hybridization. Theory and practice of nucleic acid hybridization is described, *e.g.*, in S. Agrawal (ed.) *Methods in Molecular Biology*, volume 20; and Tijssen (1993) *Laboratory Techniques in biochemistry and molecular biology-hybridization with nucleic acid probes*, *e.g.*, part I chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays," Elsevier, New York provide a basic guide to nucleic acid hybridization.

A fragment of a nucleic acid sequence is defined as a nucleotide sequence having fewer nucleotides than the nucleotide sequence encoding the full length CRT polypeptide, antigenic polypeptide, or the fusion thereof. This invention includes such nucleic acid fragments that encode polypeptides which retain the ability of the fusion polypeptide to induce increases in frequency or reactivity of T cells, including CD8+ T cells, that are specific for the antigen part of the fusion polypeptide.

Nucleic acid sequences of this invention may also include linker sequences, natural or modified restriction endonuclease sites and other sequences that are useful for manipulations related to cloning, expression or purification of encoded protein or fragments. For example, a fusion protein may comprise a linker between the antigen and the IPP protein.

Other nucleic acid vaccines that may be used include single chain trimers (SCT), as further described in the Examples and in references cited therein, all of which are specifically incorporated by reference herein.

5 *Backbone of nucleic acid vaccine*

A nucleic acid, *e.g.*, DNA vaccine may comprise an “expression vector” or “expression cassette,” *i.e.*, a nucleotide sequence which is capable of affecting expression of a protein coding sequence in a host compatible with such sequences. Expression cassettes include at least a promoter operably linked with the polypeptide coding sequence; and, optionally, with other sequences, *e.g.*, transcription termination signals. Additional factors necessary or helpful in effecting expression may also be included, *e.g.*, enhancers.

“Operably linked” means that the coding sequence is linked to a regulatory sequence in a manner that allows expression of the coding sequence. Known regulatory sequences are selected to direct expression of the desired protein in an appropriate host cell. Accordingly, the term “regulatory sequence” includes promoters, enhancers and other expression control elements. Such regulatory sequences are described in, for example, Goeddel, *Gene Expression Technology. Methods in Enzymology*, vol. 185, Academic Press, San Diego, Calif. (1990)).

A promoter region of a DNA or RNA molecule binds RNA polymerase and promotes the transcription of an “operably linked” nucleic acid sequence. As used herein, a “promoter sequence” is the nucleotide sequence of the promoter which is found on that strand of the DNA or RNA which is transcribed by the RNA polymerase. Two sequences of a nucleic acid molecule, such as a promoter and a coding sequence, are “operably linked” when they are linked to each other in a manner which permits both sequences to be transcribed onto the same RNA transcript or permits an RNA transcript begun in one sequence to be extended into the second sequence. Thus, two sequences, such as a promoter sequence and a coding sequence of DNA or RNA are operably linked if transcription commencing in the promoter sequence will produce an RNA transcript of the operably linked coding sequence. In order to be “operably linked” it is not necessary that two sequences be immediately adjacent to one another in the linear sequence.

In one embodiment, certain promoter sequences of the present invention must be operable in mammalian cells and may be either eukaryotic or viral promoters. Certain promoters are also described in the Examples, and other useful promoters and regulatory

elements are discussed below. Suitable promoters may be inducible, repressible or constitutive. A “constitutive” promoter is one which is active under most conditions encountered in the cell’s environmental and throughout development. An “inducible” promoter is one which is under environmental or developmental regulation. A “tissue specific” promoter is active in certain tissue types of an organism. An example of a constitutive promoter is the viral promoter MSV-LTR, which is efficient and active in a variety of cell types, and, in contrast to most other promoters, has the same enhancing activity in arrested and growing cells. Other viral promoters include that present in the CMV-LTR (from cytomegalovirus) (Bashart, M. *et al.*, *Cell* 41:521, 1985) or in the RSV-LTR (from Rous sarcoma virus) (Gorman, C.M., *Proc. Natl. Acad. Sci. USA* 79:6777, 1982). Also useful are the promoter of the mouse metallothionein I gene (Hamer, D, *et al.*, *J. Mol. Appl. Gen.* 1:273-88, 1982; the TK promoter of Herpes virus (McKnight, S, *Cell* 31:355-65, 1982); the SV40 early promoter (Benoist, C., *et al.*, *Nature* 290:304-10, 1981); and the yeast *gal4* gene promoter (Johnston, SA *et al.*, *Proc. Natl. Acad. Sci. USA* 79:6971-5, 1982); Silver, PA, *et al.*, *Proc. Natl. Acad. Sci. (USA)* 81:5951-5, 1984)). Other illustrative descriptions of transcriptional factor association with promoter regions and the separate activation and DNA binding of transcription factors include: Keegan *et al.*, *Nature* 231:699, 1986; Fields *et al.*, *Nature* 340:245, 1989; Jones, *Cell* 61:9, 1990; Lewin, *Cell* 61:1161, 1990; Ptashne *et al.*, *Nature* 346:329, 1990; Adams *et al.*, *Cell* 72:306, 1993.

The promoter region may further include an octamer region which may also function as a tissue specific enhancer, by interacting with certain proteins found in the specific tissue. The enhancer domain of the DNA construct of the present invention is one which is specific for the target cells to be transfected, or is highly activated by cellular factors of such target cells. Examples of vectors (plasmid or retrovirus) are disclosed, *e.g.*, in Roy-Burman *et al.*, U.S. Patent No. 5,112,767, incorporated by reference. For a general discussion of enhancers and their actions in transcription, see, Lewin, BM, *Genes IV*, Oxford University Press pp. 552-576, 1990 (or later edition). Particularly useful are retroviral enhancers (*e.g.*, viral LTR) that is placed upstream from the promoter with which it interacts to stimulate gene expression. For use with retroviral vectors, the endogenous viral LTR may be rendered enhancer-less and substituted with other desired enhancer sequences which confer tissue specificity or other desirable properties such as transcriptional efficiency.

Thus, expression cassettes include plasmids, recombinant viruses, any form of a recombinant “naked DNA” vector, and the like. A “vector” comprises a nucleic acid which can infect, transfect, transiently or permanently transduce a cell. It will be recognized that a vector can be a naked nucleic acid, or a nucleic acid complexed with protein or lipid. The vector optionally comprises viral or bacterial nucleic acids and/or proteins, and/or membranes (*e.g.*, a cell membrane, a viral lipid envelope, *etc.*). Vectors include replicons (*e.g.*, RNA replicons), bacteriophages) to which fragments of DNA may be attached and become replicated. Vectors thus include, but are not limited to RNA, autonomous self-replicating circular or linear DNA or RNA, *e.g.*, plasmids, viruses, and the like (U.S. Patent No. 5,217,879, incorporated by reference), and includes both the expression and nonexpression plasmids. Where a recombinant cell or culture is described as hosting an “expression vector” this includes both extrachromosomal circular and linear DNA and DNA that has been incorporated into the host chromosome(s). Where a vector is being maintained by a host cell, the vector may either be stably replicated by the cells during mitosis as an autonomous structure, or is incorporated within the host’s genome.

Exemplary virus vectors that may be used include recombinant adenoviruses (Horowitz, MS, In: *Virology*, Fields, BN *et al.*, eds, Raven Press, NY, 1990, p. 1679; Berkner, KL, *Biotechniques* 6:616-29, 1988; Strauss, SE, In: *The Adenoviruses*, Ginsberg, HS, ed., Plenum Press, NY, 1984, chapter 11) and herpes simplex virus (HSV). Advantages of adenovirus vectors for human gene delivery include the fact that recombination is rare, no human malignancies are known to be associated with such viruses, the adenovirus genome is double stranded DNA which can be manipulated to accept foreign genes of up to 7.5 kb in size, and live adenovirus is a safe human vaccine organisms. Adeno-associated virus is also useful for human therapy (Samulski, RJ *et al.*, *EMBO J.* 10:3941, 1991) according to the present invention.

Another vector which can express the DNA molecule of the present invention, and is useful in the present therapeutic setting is vaccinia virus, which can be rendered non-replicating (U.S. Pats. 5,225,336; 5,204,243; 5,155,020; 4,769,330; Fuerst, TR *et al.*, *Proc. Natl. Acad. Sci. USA* 86:2549-53, 1992; Chakrabarti, S *et al.*, *Mol Cell Biol* 5:3403-9, 1985, each of which are incorporated by reference). Descriptions of recombinant vaccinia viruses and other viruses containing heterologous DNA and their uses in immunization and DNA therapy are reviewed in: Moss, B, *Curr Opin Genet Dev* 3:86-90, 1993; Moss, B, *Biotechnol.* 20:345-62, 1992).

Other viral vectors that may be used include viral or non-viral vectors, including adeno-associated virus vectors, retrovirus vectors, lentivirus vectors, and plasmid vectors. Exemplary types of viruses include HSV (herpes simplex virus), AAV (adeno associated virus), HIV (human immunodeficiency virus), BIV (bovine immunodeficiency virus), and
5 MLV (murine leukemia virus).

A DNA vaccine may also use a replicon, *e.g.*, an RNA replicon, a self-replicating RNA vector. In one embodiment, a replicon is one based on a Sindbis virus RNA replicon, *e.g.*, SINrep5. The present inventors tested E7 in the context of such a vaccine and showed (see Wu *et al.*, U.S. Patent Application 10/343,719) that a Sindbis virus RNA vaccine
10 encoding HSV-1 VP22 linked to E7 significantly increased activation of E7-specific CD8 T cells, resulting in potent antitumor immunity against E7-expressing tumors. The Sindbis virus RNA replicon vector used in these studies, SINrep5, has been described (Bredenbeek, P J *et al.*, 1993, J. Virol. 67:6439-6446).

Generally, RNA replicon vaccines may be derived from alphavirus vectors, such as
15 Sindbis virus (Hariharan, M J *et al.*, 1998. J Virol 72:950-8.), Semliki Forest virus (Berglund, P M *et al.*, 1997. AIDS Res Hum Retroviruses 13:1487-95; Ying, H T *et al.*, 1999. Nat Med 5:823-7) or Venezuelan equine encephalitis virus (Pushko, P M *et al.*, 1997. Virology 239:389-401). These self-replicating and self-limiting vaccines may be administered as either (1) RNA or (2) DNA which is then transcribed into RNA replicons in
20 cells transfected in vitro or in vivo (Berglund, P C *et al.*, 1998. Nat Biotechnol 16:562-5; Leitner, W W *et al.*, 2000. Cancer Res 60:51-5). An exemplary Semliki Forest virus is pSCA1 (DiCiommo, D P *et al.*, J Biol Chem 1998; 273:18060-6).

The plasmid vector pcDNA3 or a functional homolog thereof (SEQ ID NO: 1) may be used in a DNA vaccine. In other embodiments, pNGVL4a (SEQ ID NO: 2) is used.

25 pNGVL4a, one plasmid backbone for the present invention was originally derived from the pNGVL3 vector, which has been approved for human vaccine trials. The pNGVL4a vector includes two immunostimulatory sequences (tandem repeats of CpG dinucleotides) in the noncoding region. Whereas any other plasmid DNA that can transform either APCs, including DC's or other cells which, via cross-priming, transfer the
30 antigenic moiety to DCs, is useful in the present invention, pNGFVLA4a may be used because of the fact that it has already been approved for human therapeutic use.

The following references set forth principles and current information in the field of basic, medical and veterinary virology and are incorporated by reference: *Fields Virology*,

Fields, BN *et al.*, eds., Lippincott Williams & Wilkins, NY, 1996; *Principles of Virology: Molecular Biology, Pathogenesis, and Control*, Flint, S.J. *et al.*, eds., Amer Soc Microbiol, Washington DC, 1999; *Principles and Practice of Clinical Virology*, 4th Edition, Zuckerman. A.J. *et al.*, eds, John Wiley & Sons, NY, 1999; *The Hepatitis C Viruses*, by Hagedorn, CH *et al.*, eds., Springer Verlag, 1999; *Hepatitis B Virus: Molecular Mechanisms in Disease and Novel Strategies for Therapy*, Koshy, R. *et al.*, eds, World Scientific Pub Co, 1998; *Veterinary Virology*, Murphy, F.A. *et al.*, eds., Academic Press, NY, 1999; *Avian Viruses: Function and Control*, Ritchie, B.W., Iowa State University Press, Ames, 2000; *Virus Taxonomy: Classification and Nomenclature of Viruses: Seventh Report of the International Committee on Taxonomy of Viruses*, by M. H. V. Van Regenmortel, MHV *et al.*, eds., Academic Press; NY, 2000.

In addition to naked DNA or viral vectors, engineered bacteria may be used as vectors. A number of bacterial strains including *Salmonella*, BCG and *Listeria monocytogenes*(LM) (Hoiseth *et al.*, *Nature* 291:238-9, 1981; Poirier, TP *et al.*, *J Exp Med* 168:25-32, 1988); Sadoff, JC *et al.*, *Science* 240:336-8, 1988; Stover, CK *et al.*, *Nature* 351:456-60, 1991; Aldovini, A *et al.*, *Nature* 351:479-82, 1991). These organisms display two promising characteristics for use as vaccine vectors: (1) enteric routes of infection, providing the possibility of oral vaccine delivery; and (2) infection of monocytes/macrophages thereby targeting antigens to professional APCs.

In addition to virus-mediated gene transfer *in vivo*, physical means well-known in the art can be used for direct transfer of DNA, including administration of plasmid DNA (Wolff *et al.*, 1990, *supra*) and particle-bombardment mediated gene transfer (Yang, N-S, *et al.*, *Proc Natl Acad Sci USA* 87:9568, 1990; Williams, RS *et al.*, *Proc Natl Acad Sci USA* 88:2726, 1991; Zelenin, AV *et al.*, *FEBS Lett* 280:94, 1991; Zelenin, AV *et al.*, *FEBS Lett* 244:65, 1989); Johnston, SA *et al.*, *In Vitro Cell Dev Biol* 27:11, 1991). Furthermore, electroporation, a well-known means to transfer genes into cells *in vitro*, can be used to transfer DNA molecules according to the present invention to tissues *in vivo* (Titomirov, AV *et al.*, *Biochim Biophys Acta* 1088:131, 1991).

“Carrier mediated gene transfer” has also been described (Wu, CH *et al.*, *J Biol Chem* 264:16985, 1989; Wu, GY *et al.*, *J Biol Chem* 263:14621, 1988; Soriano, P *et al.*, *Proc Nat. Acad Sci USA* 80:7128, 1983; Wang, C-Y *et al.*, *Pro. Natl Acad Sci USA* 84:7851, 1982; Wilson, JM *et al.*, *J Biol Chem* 267:963, 1992). In one embodiment, carriers are targeted liposomes (Nicolau, C *et al.*, *Proc Natl Acad Sci USA* 80:1068, 1983;

Soriano *et al.*, *supra*) such as immunoliposomes, which can incorporate acylated mAbs into the lipid bilayer (Wang *et al.*, *supra*). Polycations such as asialoglycoprotein/polylysine (Wu *et al.*, 1989, *supra*) may be used, where the conjugate includes a target tissue-recognizing molecule (*e.g.*, asialo-orosomucoid for liver) and a DNA binding compound to
5 bind to the DNA to be transfected without causing damage, such as polylysine. This conjugate is then complexed with plasmid DNA of the present invention.

Plasmid DNA used for transfection or microinjection may be prepared using methods well-known in the art, for example using the Quiagen procedure (Quiagen), followed by DNA purification using known methods, such as the methods exemplified
10 herein.

Such expression vectors may be used to transfect host cells (*in vitro*, *ex vivo* or *in vivo*) for expression of the DNA and production of the encoded proteins which include fusion proteins or peptides. In one embodiment, a DNA vaccine is administered to or contacted with a cell, *e.g.*, a cell obtained from a subject (*e.g.*, an antigen presenting cell),
15 and administered to a subject, wherein the subject is treated before, after or at the same time as the cells are administered to the subject.

The term "isolated" as used herein, when referring to a molecule or composition, such as a translocation polypeptide or a nucleic acid coding therefor, means that the molecule or composition is separated from at least one other compound (protein, other
20 nucleic acid, *etc.*) or from other contaminants with which it is natively associated or becomes associated during processing. An isolated composition can also be substantially pure. An isolated composition can be in a homogeneous state and can be dry or in aqueous solution. Purity and homogeneity can be determined, for example, using analytical chemical techniques such as polyacrylamide gel electrophoresis (PAGE) or high
25 performance liquid chromatography (HPLC). Even where a protein has been isolated so as to appear as a homogenous or dominant band in a gel pattern, there are trace contaminants which co-purify with it.

Host cells transformed or transfected to express the fusion polypeptide or a homologue or functional derivative thereof are within the scope of the invention. For
30 example, the fusion polypeptide may be expressed in yeast, or mammalian cells such as Chinese hamster ovary cells (CHO) or human cells. In one embodiment, cells for expression according to the present invention are APCs or DCs. Other suitable host cells are known to those skilled in the art.

Other nucleic acids for potentiating immune responses

Methods of administering a chemotherapeutic drug and a vaccine may further comprise administration of one or more other constructs, *e.g.*, to prolong the life of antigen presenting cells. Exemplary constructs are described in the following two sections. Such constructs may be administered simultaneously or at the same time as a DNA vaccine. Alternatively, they may be administered before or after administration of the DNA vaccine or chemotherapeutic drug.

Potential of immune responses using siRNA directed at apoptotic pathways

Administration to a subject of a DNA vaccine and a chemotherapeutic drug may be accompanied by administration of one or more other agents, *e.g.*, constructs. In one embodiment, a method comprises further administering to a subject an siRNA directed at an apoptotic pathway, such as described in WO 2006/073970, which is incorporated herein in its entirety.

The present inventors have previously designed siRNA sequences that hybridize to, and block expression of the activation of Bak and Bax proteins that are central players in the apoptosis signalling pathway. The present invention is also directed to the methods of treating tumors or hyper proliferative disease involving the administration of siRNA molecules (sequences), vectors containing or encoding the siRNA, expression vectors with a promoter operably linked to the siRNA coding sequence that drives transcription of siRNA sequences that are "specific" for sequences Bak and Bax nucleic acid. siRNAs may include single stranded "hairpin" sequences because of their stability and binding to the target mRNA.

Since Bak and Bax are involved, among other death proteins, in apoptosis of APCs, particularly DCs, the present siRNA sequences may be used in conjunction with a broad range of DNA vaccine constructs encoding antigens to enhance and promote the immune response induced by such DNA vaccine constructs, particularly CD8⁺ T cell mediated immune responses typified by CTL activation and action. This is believed to occur as a result of the effect of the siRNA in prolonging the life of antigen-presenting DCs which may otherwise be killed in the course of a developing immune response by the very same CTLs that the DCs are responsible for inducing.

In addition to Bak and Bax, additional targets for siRNAs designed in an analogous manner include caspase 8, caspase 9 and caspase 3. The present invention includes compositions and methods in which siRNAs targeting any two or more of Bak, Bax, caspase 8,

caspase 9 and caspase 3 are used in combination, optionally simultaneously (along with a DNA immunogen that encodes an antigen), to administer to a subject. Such combinations of siRNAs may also be used to transfect DCs (along with antigen loading) to improve the immunogenicity of the DCs as cellular vaccines by rendering them resistant to apoptosis.

5 siRNAs suppress gene expression through a highly regulated enzyme-mediated process called RNA interference (RNAi) (Sharp, P.A., *Genes Dev.* 15:485–90, 2001; Bernstein, E *et al.*, *Nature* 409:363–66, 2001; Nykanen, A *et al.*, *Cell* 107:309–21, 2001; Elbashir *et al.*, *Genes Dev.* 15:188–200, 2001). RNA interference is the sequence-specific degradation of homologues in an mRNA of a targeting sequence in an siNA. As used
10 herein, the term siNA (small, or short, interfering nucleic acid) is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi (RNA interference), for example short (or small) interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified
15 oligonucleotide, chemically-modified siRNA, post-transcriptional gene silencing RNA (ptgsRNA), translational silencing, and others. RNAi involves multiple RNA-protein interactions characterized by four major steps: assembly of siRNA with the RNA-induced silencing complex (RISC), activation of the RISC, target recognition and target cleavage. These interactions may bias strand selection during siRNA-RISC assembly and activation,
20 and contribute to the overall efficiency of RNAi (Khvorova, A *et al.*, *Cell* 115:209–216 (2003); Schwarz, DS *et al.* 115:199–208 (2003))

 Considerations to be taken into account when designing an RNAi molecule include, among others, the sequence to be targeted, secondary structure of the RNA target and binding of RNA binding proteins. Methods of optimizing siRNA sequences will be evident
25 to the skilled worker. Typical algorithms and methods are described in Vickers *et al.* (2003) *J Biol Chem* 278:7108-7118; Yang *et al.* (2003) *Proc Natl Acad Sci USA* 99:9942-9947; Far *et al.* (2003) *Nuc. Acids Res.* 31:4417-4424; and Reynolds *et al.* (2004) *Nature Biotechnology* 22:326-330, all of which are incorporated by reference in their entirety.

 The methods described in Far *et al.*, *supra*, and Reynolds *et al.*, *supra*, may be used
30 by those of ordinary skill in the art to select targeted sequences and design siRNA sequences that are effective at silencing the transcription of the relevant mRNA. Far *et al.* suggests options for assessing target accessibility for siRNA and supports the design of active siRNA constructs. This approach can be automated, adapted to high throughput and

is open to include additional parameters relevant to the biological activity of siRNA. To identify siRNA-specific features likely to contribute to efficient processing at each of the steps of RNAi noted above. Reynolds *et al.*, *supra*, present a systematic analysis of 180 siRNAs targeting the mRNA of two genes. Eight characteristics associated with siRNA functionality were identified: low G/C content, a bias towards low internal stability at the sense strand 3'-terminus, lack of inverted repeats, and sense strand base preferences (positions 3, 10, 13 and 19). Application of an algorithm incorporating all eight criteria significantly improves potent siRNA selection. This highlights the utility of rational design for selecting potent siRNAs that facilitate functional gene knockdown.

Candidate siRNA sequences against mouse and human Bax and Bak are selected using a process that involves running a BLAST search against the sequence of Bax or Bak (or any other target) and selecting sequences that "survive" to ensure that these sequences will not be cross matched with any other genes.

siRNA sequences selected according to such a process and algorithm may be cloned into an expression plasmid and tested for their activity in abrogating Bak/Bax function cells of the appropriate animal species. Those sequences that show RNAi activity may be used by direct administration bound to particles, or recloned into a viral vector such as a replication-defective human adenovirus serotype 5 (Ad5).

One advantage of this viral vector is the high titer obtainable (in the range of 10^{10}) and therefore the high multiplicities-of infection that can be attained. For example, infection with 100 infectious units/ cell ensures all cells are infected. Another advantage of this virus is the high susceptibility and infectivity and the host range (with respect to cell types). Even if expression is transient, cells would survive, possibly replicate, and continue to function before Bak/Bax activity would recover and lead to cell death. In one embodiment, constructs include the following:

For **Bak**:

5'-UGCCUACGAACUCUUCACCCdTdT-3' (sense) (SEQ ID NO: 42)

5'-GGUGAAGAGUUCGUAGGCAdTdT-3' (antisense) (SEQ ID NO: 43),

The nucleotide sequence encoding the Bak protein (including the stop codon) (GenBank accession No. NM_007523 is shown below (SEQ ID NO: 44) with the targeted sequence in upper case, underscored.

atggcatctggacaaggaccagggtccccgaaggtgggctgcatgaggtccccgtccccttctgaacagcaggtgtcccaggac
acagaggagggtcttcgaagctacgtttttacctccaccagcaggaacaggagaccaggggcgccgcctgccaaaccccgag

atggacaacttgcccctggaaccaacagcatcttgggtcaggtgggtcggcagcttgctctcatcgagatgatattaaccggcg
 ctacgacacagagttccagaatttactagaacagcttcagcccacagccgggaa TGCCTACGAACTCTTCACC
 aagatcgctccagcctatttaagagtggcatcagctggggccgctgggtggctctcctgggctttggctaccgtctggccctgtac
 gtctaccagcgtggtttgaccggcttctgggccaggtgacctgcttttggctgatatcatactgcatcattacatcgccagatggatc
 5 gcacagagagggcggttgggtggcagccctgaatttgcgtagagaccccatcctgaccgtaatggtgatttttgggtgtggttctgttgg
 gccaatcgtgtgtacacagattcttcagatcatga 637

The targeted sequence of Bak, TGCCTACGAACTCTTCACC is SEQ ID NO: 45

For Bax:

10 5'P-UAUGGAGCUGCAGAGGAUGdTdT-3' (sense) (SEQ ID NO: 46)

5'P-CAUCCUCUGCAGCUCCAUAdTdT-3' (antisense) (SEQ ID NO: 47)

The nucleotide sequence encoding Bax (including the stop codon) (GenBank accession No. L22472 is shown below (SEQ ID NO: 48) with the targeted sequence shown in upper case and underscored

15 atggacgggtccggggagcagcttgggagcggcgggcccaccagctctgaacagatcatgaagacaggggccttttctacag
 ggtttcatccaggatcgagcagggaggatggctggggagacacctgagctgaccttggagcagccgcccaggatgcgtccacc
 aagaagctgagcgagtgtctccggcgaattggagatgaactggatagcaa TATGGAGCTGCAGAGGATGatt
 gctgacgtggacacggactcccccgagaggtcttctccgggtggcagctgacatgtttgctgatggcaactcaactggggccg
 cgtggttgcctcttctactttgctagcaactggtgctcaaggccctgtgcactaaagtgcccgagctgatcagaaccatcatgggc
 20 tggacactggacttctcctgtagcggtgcttcttgatccaagaccaggggtggctgggaaggcctctctctacttcgggacc
 cccacatggcagacagtaccatcttgggtggagtcctcaccgcctcgtcaccatctggaagaagatgggctga 589

The targeted sequence of Bax, TATGGAGCTGCAGAGGATG is SEQ ID NO: 49

In a one embodiment, the inhibitory molecule is a double stranded nucleic acid (i.e., an RNA), used in a method of RNA interference. The following show the "paired" 19

25 nucleotide structures of the siRNA sequences shown above, where the symbol $\updownarrow$:

Bak: 5'P- UGCCUACGAACUCUUCACCDdTdT-3' (sense) (SEQ ID NO: 42)

$\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow$

3'P-dTdtACGGAUGCUUGAGAAGUGG -5' (antisense)(SEQ ID NO: 43)

Bax: 5'P- UAUGGAGCUGCAGAGGAUGdTdT-3' (sense) (SEQ ID NO: 46)

30 $\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow\updownarrow$

3'P-dTdTAUACCUCGACGUCUCCUAC -5' (antisense)(SEQ ID NO: 47)

Other Pro-Apoptotic Proteins to be Targeted

1. Caspase 8: The nucleotide sequence of human caspase-8 is shown below (SEQ ID NO: 50). GenBank Access. # NM_001228. One target sequence for RNAi is underscored. Others may be identified using methods such as those described herein (and in reference cited herein, primarily Far *et al.*, *supra* and Reynolds *et al.*, *supra*).

atg gac ttc agc aga aat ctt tat gat att ggg gaa caa ctg gac agt gaa gat ctg gcc tcc ctc aag ttc
ctg agc ctg gac tac att ccg caa agg aag caa gaa ccc atc aag gat gcc ttg atg tta ttc cag aga ctc
cag gaa aag aga atg ttg gag gaa agc aat ctg tcc ttc ctg aag gag ctg ctc ttc cga att aat aga ctg
gat ttg ctg att acc tac cta aac act aga aag gag gag atg gaa agg gaa ctt cag aca cca ggc agg gct
10 caa att tct gcc tac agg ttc cac ttc tgc cgc atg agc tgg gct gaa gca aac agc cag tgc cag aca cag
tct gta cct ttc tgg cgg agg gtc gat cat cta tta ata agg gtc atg ctc tat cag att tca gaa gaa gtg agc
aga tca gaa ttg agg tct ttt aag ttt ctt ttg caa gag gaa atc tcc aaa tgc aaa ctg gat gat gac atg aac
ctg ctg gat att ttc ata gag atg gag aag agg gtc atc ctg gga gaa gga aag ttg gac atc ctg aaa aga
gtc tgt gcc caa atc aac aag agc ctg ctg aag ata atc aac gac tat gaa gaa ttc agc aaa ggg gag gag
15 ttg tgt ggg gta atg aca atc tcg gac tct cca aga gaa cag gat agt gaa tca cag act ttg gac aaa gtt
tac caa atg aaa agc aaa cct cgg gga tac tgt ctg atc atc aac aat cac aat ttt gca aaa gca cgg gag
aaa gtg ccc aaa ctt cac agc att agg gac agg aat gga aca cac ttg gat gca ggg gct ttg acc acg acc
ttt gaa gag ctt cat ttt gag atc aag ccc cac gat gac tgc aca gta gag caa atc tat gag att ttg aaa atc
tac caa ctc atg gac cac agt aac atg gac tgc ttc atc tgc tgt atc ctc tcc cat gga gac aag ggc atc
20 atc tat ggc act gat gga cag gag gcc ccc atc tat gag ctg aca tct cag ttc act ggt ttg aag tgc cct
tcc ctt gct gga aaa ccc aaa gtg ttt ttt att cag gct tgt cag ggg gat aac tac cag aaa ggt ata cct gtt
gag act gat tca gag gag caa ccc tat tta gaa atg gat tta tca tca cct caa acg aga tat atc ccg gat
gag gct gac ttt ctg ctg ggg atg gcc act gtg aat aac tgt gtt tcc tac cga aac cct gca gag gga acc
tgg tac atc cag tca ctt tgc cag agc ctg aga gag cga tgt cct cga ggc gat gat att ctc acc atc ctg
25 act gaa gtg aac tat gaa gta agc aac aag gat gac aag aaa aac atg ggg aaa cag atg cct cag cct
act ttc aca cta aga aaa aaa ctt gtc ttc cct tct gat *tga* **1491**

The sequences of sense and antisense siRNA strands for targeting this sequence (including dTdT 3' overhangs, are:

5'-AACCUCGGGGAUACUGUCUGAdTdT-3' (sense) (SEQ ID NO: 51)

30 5'-UCAGACAGUAUCCCCGAGGUUdTdT-3' (antisense) (SEQ ID NO: 52)

2. Caspase 9: The nucleotide sequence of human caspase-9 is shown below (SEQ ID NO: 53). See GenBank Access. # NM_001229. The sequence below is of "variant α " which is longer than a second alternatively spliced variant β , which lacks the underscored

part of the sequence shown below (and which is anti-apoptotic). Target sequences for RNAi, expected to fall in the underscored segment, are identified using known methods such as those described herein and in Far *et al.*, *supra* and Reynolds *et al.*, *supra*) and siNAs, such as siRNAs, are designed accordingly.

5 atg gac gaa gcg gat cgg cgg ctc ctg cgg cgg tgc cgg ctg cgg ctg gtg gaa gag ctg cag gtg gac
cag ctc tgg gac gcc ctg ctg agc cgc gag ctg ttc agg ccc cat atg atc gag gac atc cag cgg gca
ggc tct gga tct cgg cgg gat cag gcc agg cag ctg atc ata gat ctg gag act cga ggg agt cag gct ctt
cct ttg ttc atc tcc tgc tta gag gac aca ggc cag gac atg ctg gct tgc ttt ctg cga act aac agg caa
gca gca aag ttg tgc aag cca acc cta gaa aac ctt acc cca gtg gtg ctc aga cca gag att cgc aaa cca
10 gag gtt ctc aga ccg gaa aca ccc aga cca gtg gac att ggt tct gga gga ttt ggt gat gtc ggt gct ctt
gag agt ttg agg gga aat gca gat ttg gct tac atc ctg agc atg gag ccc tgt ggc cac tgc ctc att atc
aac aat gtg aac ttc tgc cgt gag tcc ggg ctc cgc acc cgc act ggc tcc aac atc gac tgt gag aag ttg
cgg cgt cgc ttc tcc tgc ctg cat ttc atg gtg gag gtg aag ggc gac ctg act gcc aag aaa atg gtg ctg
gct ttg ctg gag ctg ggc cag cag gac cac ggt gct ctg gac tgc tgc gtg gtg gtc att ctc tct cac ggc
15 tgt cag gcc agc cac ctg cag ttc cca ggg gct gtc tac ggc aca gat gga tgc cct gtg tgc gtc gag aag
att gtg aac atc ttc aat ggg acc agc tgc ccc agc ctg gga ggg aag ccc aag ctc ttt ttc atc cag gcc
tgt ggt ggg gag cag aaa gac cat ggg ttt gag gtg gcc tcc act tcc cct gaa gac gag tcc cct ggc agt
aac ccc gag cca gat gcc acc ccg ttc cag gaa ggt ttg agg acc ttc gac cag ctg gac gcc ata tct agt
ttg ccc aca ccc agt gac atc ttt gtg tcc tac tct act ttc cca ggt ttt gtt tcc tgg agg gac ccc aag agt
20 ggc tcc tgg tac gtt gag acc ctg gac gac atc ttt gag cag tgg gct cac tct gaa gac ctg cag tcc ctc
ctg ctt agg gtc gct aat gct gtt tgc gtg aaa ggg att tat aaa cag atg cct ggt tgc ttt aat ttc ctc cgg
aaa aaa ctt ttc ttt aaa aca tca **taa 1191**

3. Caspase 3: The nucleotide sequence of human caspase-3 is shown below (SEQ ID NO: 54). See GenBank Access. # NM_004346. The sequence below is of “variant α”
25 which is the longer of two alternatively spliced variants, all of which encode the full
protein. Target sequences for RNAi are identified using known methods such as those
described herein and in Far *et al.*, *supra* and Reynolds *et al.*, *supra*) and siNAs, such as
siRNAs, are designed accordingly.

atg gag aac act gaa aac tca gtg gat tca aaa tcc att aaa aat ttg gaa cca aag atc ata cat gga agc
30 gaa tca atg gac tct gga ata tcc ctg gac aac agt tat aaa atg gat tat cct gag atg ggt tta tgt ata ata
att aat aat aag aat ttt cat aaa agc act gga atg aca tct cgg tct ggt aca gat gtc gat gca gca aac ctc
agg gaa aca ttc aga aac ttg aaa tat gaa gtc agg aat aaa aat gat ctt aca cgt gaa gaa att gtg gaa
ttg atg cgt gat gtt tct aaa gaa gat cac agc aaa agg agc agt ttt gtt tgt gtg ctt ctg agc cat ggt gaa

gaa gga ata att ttt gga aca aat gga cct gtt gac ctg aaa aaa ata aca aac ttt ttc aga ggg gat cgt tgt
 aga agt cta act gga aaa ccc aaa ctt ttc att att cag gcc tgc cgt ggt aca gaa ctg gac tgt ggc att
 gag aca gac agt ggt gtt gat gat gac atg gcg tgt cat aaa ata cca gtg gag gcc gac ttc ttg tat gca
 tac tcc aca gca cct ggt tat tat tct tgg cga aat tca aag gat ggc tcc tgg ttc atc cag tgc ctt tgt gcc
 5 atg ctg aaa cag tat gcc gac aag ctt gaa ttt atg cac att ctt acc cgg gtt aac cga aag gtg gca aca
 gaa ttt gag tcc ttt tcc ttt gac gct act ttt cat gca aag aaa cag att cca tgt att gtt tcc atg ctc aca
 aaa gaa ctc tat ttt tat cac taa **834**

Long double stranded interfering RNAs, such a miRNAs, appear to tolerate mismatches more readily than do short double stranded RNAs. In addition, as used herein,
 10 the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, or an epigenetic phenomenon. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the
 15 invention can result from siNA mediated modification of chromatin structure and thereby alter gene expression (see, for example, Allshire *Science* 297:1818-19, 2002; Volpe *et al.*, *Science* 297:1833-37, 2002; Jenuwein, *Science* 297:2215-18, 2002; and Hall *et al.*, *Science* 297, 2232-2237, 2002.)

An siNA can be designed to target any region of the coding or non-coding sequence
 20 of an mRNA. An siNA is a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region has a nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from
 25 two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary. The siNA can be assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a hairpin secondary
 30 structure, having self-complementary sense and antisense regions. The siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA

molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (or can be an siNA molecule that does not require the presence within the siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.* (2002) *Cell* 110, 563-574 and Schwarz *et al.* (2002) *Molecular Cell* 10, 537-568), or 5',3'-diphosphate.

In certain embodiments, the siNA molecule of the invention comprises separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, Van der Waal's interactions, hydrophobic interactions, and/or stacking interactions.

As used herein, siNA molecules need not be limited to those molecules containing only ribonucleotides but may also further encompass deoxyribonucleotides (as in the siRNAs which each include a dTdT dinucleotide) chemically-modified nucleotides, and non-nucleotides. In certain embodiments, the siNA molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. In certain embodiments, siNAs do not require the presence of nucleotides having a 2'-hydroxy group for mediating RNAi and as such, siNAs of the invention optionally do not include any ribonucleotides (*e.g.*, nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. If modified, the siNAs of the invention can also be referred to as "short interfering modified oligonucleotides" or "siMON." Other chemical modifications, *e.g.*, as described in Int'l Patent Publications WO 03/070918 and WO 03/074654, both of which are incorporated by reference, can be applied to any siNA sequence of the invention.

In one embodiment a molecule mediating RNAi has a 2 nucleotide 3' overhang (dTdT in the sequences disclosed herein). If the RNAi molecule is expressed in a cell from a construct, for example from a hairpin molecule or from an inverted repeat of the desired sequence, then the endogenous cellular machinery will create the overhangs.

Methods of making siRNAs are conventional. *In vitro* methods include processing the polyribonucleotide sequence in a cell-free system (*e.g.*, digesting long dsRNAs with RNase III or Dicer), transcribing recombinant double stranded DNA *in vitro*, and chemical synthesis of nucleotide sequences homologous to Bak or Bax sequences. See, *e.g.*, Tuschl
 5 *et al.*, *Genes & Dev.* 13:3191-3197, 1999. *In vivo* methods include

- (1) transfecting DNA vectors into a cell such that a substrate is converted into siRNA *in vivo*. See, for example, Kawasaki *et al.*, *Nucleic Acids Res* 31:700-07, 2003;; Miyagishi *et al.*, *Nature Biotechnol* 20:497-500, 2003;; Lee *et al.*, *Nature Biotechnol* 20:500-05, 2002; Brummelkamp *et al.*, *Science* 296:550-53, 2002; McManus *et al.*,
 10 *RNA* 8:842-50, 2002; Paddison *et al.*, *Genes Dev* 16:948-58, 2002; Paddison *et al.*, *Proc Natl Acad Sci USA* 99:1443-48, 2002; Paul *et al.*, *Nature Biotechnol* 20:505-08, 2002; Sui *et al.*, *Proc Natl Acad Sci USA* 99:5515-20, 2002; Yu *et al.*, *Proc Natl Acad Sci USA* 99:6047-52, 2002)
- (2) expressing short hairpin RNAs from plasmid systems using RNA polymerase III (pol
 15 III) promoters. See, for example, Kawasaki *et al.*, *supra*; Miyagishi *et al.*, *supra*; Lee *et al.*, *supra*; Brummelkamp *et al.*, *supra*; McManus *et al.*, *supra*), Paddison *et al.*, *supra* (both); Paul *et al.*, *supra*, Sui *et al.*, *supra*; and Yu *et al.*, *supra*; and/or
- (3) expressing short RNA from tandem promoters. See, for example, Miyagishi *et al.*, *supra*; Lee *et al.*, *supra*).

20 When synthesized *in vitro*, a typical micromolar scale RNA synthesis provides about 1 mg of siRNA, which is sufficient for about 1000 transfection experiments using a 24-well tissue culture plate format. In general, to inhibit Bak or Bax expression in cells in culture, one or more siRNAs can be added to cells in culture media, typically at about 1 ng/ml to about 10 µg siRNA/ml.

25 For reviews and more general description of inhibitory RNAs, see Lau *et al.*, *Sci Amer* Aug 2003: 34-41; McManus *et al.*, *Nature Rev Genetics* 3, 737-47, 2002; and Dykxhoorn *et al.*, *Nature Rev Mol Cell Bio* 4:457-467, 2003. For further guidance regarding methods of designing and preparing siRNAs, testing them for efficacy, and using them in methods of RNA interference (both *in vitro* and *in vivo*), see, *e.g.*, Allshire, *Science*
 30 297:1818-19, 2002; Volpe *et al.*, *Science* 297:1833-37, 2002; Jenuwein, *Science* 297:2215-18, 2002; Hall *et al.*, *Science* 297 2232-37, 2002; Hutvagner *et al.*, *Science* 297:2056-60, 2002; McManus *et al.* *RNA* 8:842-850, 2002; Reinhart *et al.*, *Genes Dev.* 16:1616-26, 2002; Reinhart *et al.*, *Science* 297:1831, 2002; Fire *et al.* (1998) *Nature* 391:806-11, 2002; Moss,

Curr Biol 11:R772-5, 2002; Brummelkamp *et al.*, *supra*; Bass, *Nature* 411 428-9, 2001; Elbashir *et al.*, *Nature* 411:494-8; US Pat. 6,506,559; Published US Pat App. 20030206887; and PCT applications WO99/07409, WO99/32619, WO 00/01846, WO 00/44914, WO00/44895, WO01/29058, WO01/36646, WO01/75164, WO01/92513, WO 01/29058, 5 WO01/89304, WO01/90401, WO02/16620, and WO02/29858, all of which are incorporated by reference.

Ribozymes and siNAs can take any of the forms, including modified versions, described for antisense nucleic acid molecules; and they can be introduced into cells as oligonucleotides (single or double stranded), or in the form of an expression vector.

10 In one embodiment, an antisense nucleic acid, siNA (*e.g.*, siRNA) or ribozyme comprises a single stranded polynucleotide comprising a sequence that is at least about 90% (*e.g.*, at least about 93%, 95%, 97%, 98% or 99%) identical to a target segment (such as those indicted for Bak and Bax above) or a complement thereof. As used herein, a DNA and an RNA encoded by it are said to contain the same "sequence," taking into account that 15 the thymine bases in DNA are replaced by uracil bases in RNA.

Active variants (*e.g.*, length variants, including fragments; and sequence variants) of the nucleic acid-based inhibitors discussed herein are also within the scope of the invention. An "active" variant is one that retains an activity of the inhibitor from which it is derived (*i.e.*, the ability to inhibit expression). It is to test a variant to determine for its activity 20 using conventional procedures.

As for length variants, an antisense nucleic acid or siRNA may be of any length that is effective for inhibition of a gene of interest. Typically, an antisense nucleic acid is between about 6 and about 50 nucleotides (*e.g.*, at least about 12, 15, 20, 25, 30, 35, 40, 45 or 50 nt), and may be as long as about 100 to about 200 nucleotides or more. Antisense 25 nucleic acids having about the same length as the gene or coding sequence to be inhibited may be used. When referring to length, the terms bases and base pairs (bp) are used interchangeably, and will be understood to correspond to single stranded (ss) and double stranded (ds) nucleic acids. The length of an effective siNA is generally between about 15 bp and about 29 bp in length, between about 19 and about 29 bp (*e.g.*, about 15, 17, 19, 21, 30 23, 25, 27 or 29 bp), with shorter and longer sequences being acceptable. Generally, siNAs are shorter than about 30 bases to prevent eliciting interferon effects. For example, an active variant of an siRNA having, for one of its strands, the 19 nucleotide sequence of any of SEQ ID NOs: 42, 43, 46, and 47 herein can lack base pairs from either, or both, of ends

of the dsRNA; or can comprise additional base pairs at either, or both, ends of the ds RNA, provided that the total of length of the siRNA is between about 19 and about 29 bp, inclusive. One embodiment of the invention is an siRNA that “consists essentially of” sequences represented by SEQ ID NOs: 42, 43, 46, and 47 or complements of these
5 sequence. The term “consists essentially of” is an intermediate transitional phrase, and in this case excludes, for example, sequences that are long enough to induce a significant interferon response. An siRNA of the invention may consist essentially of between about 19 and about 29 bp in length.

As for sequence variants, in one embodiment, an inhibitory nucleic acid, whether an
10 antisense molecule, a ribozyme (the recognition sequences), or an siNA, comprises a strand that is complementary (100% identical in sequence) to a sequence of a gene that it is designed to inhibit. However, 100% sequence identity is not required to practice the present invention. Thus, the invention has the advantage of being able to tolerate naturally occurring sequence variations, for example, in human c-met, that might be expected due to
15 genetic mutation, polymorphism, or evolutionary divergence. Alternatively, the variant sequences may be artificially generated. Nucleic acid sequences with small insertions, deletions, or single point mutations relative to the target sequence can be effective inhibitors.

The degree of sequence identity may be optimized by sequence comparison and
20 alignment algorithms well-known in the art (see Gribskov and Devereux, Sequence Analysis Primer, Stockton Press, 1991, and references cited therein) and calculating the percent difference between the nucleotide sequences by, for example, the Smith-Waterman algorithm as implemented in the BESTFIT software program using default parameters (*e.g.*, University of Wisconsin Genetic Computing Group). In one embodiment, at least about
25 90% sequence identity may be used (*e.g.*, at least about 92%, 95%, 98% or 99%), or even 100% sequence identity, between the inhibitory nucleic acid and the targeted sequence of targeted gene.

Alternatively, an active variant of an inhibitory nucleic acid of the invention is one that hybridizes to the sequence it is intended to inhibit under conditions of high stringency.
30 For example, the duplex region of an siRNA may be defined functionally as a nucleotide sequence that is capable of hybridizing with a portion of the target gene transcript under high stringency conditions (*e.g.*, 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50°C or 70°C, hybridization for 12-16 hours), followed generally by washing.

DC-1 cells or BM-DCs presenting a given antigen X, when not treated with the siRNAs of the invention, respond to sufficient numbers X-specific CD8⁺ CTL by apoptotic cell death. In contrast, the same cells transfected with the siRNA or infected with a viral vector encoding the present siRNA sequences survive better despite the delivery of killing signals.

Delivery and expression of the siRNA compositions of the present invention inhibit the death of DCs *in vivo* in the process of a developing T cell response, and thereby promote and stimulate the generation of an immune response induced by immunization with an antigen-encoding DNA vaccine vector. These capabilities have been exemplified by showing that:

- (1) co-administration of DNA vaccines encoding HPV-16 E7 with siRNA targeted to Bak and Bax prolongs the lives of antigen-presenting DCs in the draining lymph nodes, thereby enhancing antigen-specific CD8⁺ T cell responses, and eliciting potent antitumor effects against an E7-expressing tumor in vaccinated subjects.
- (2) DCs transfected with siRNA targeting Bak and Bax resist killing by T cells *in vivo*. E7-loaded DCs transfected with Bak/Bax siRNA so that Bak and Bax protein expression is downregulated resist apoptotic death induced by T cells *in vivo*. When administered to subjects, these DCs generate stronger antigen-specific immune responses and manifest therapeutic effects (compared to DCs transfected with control siRNA).

Thus, siRNA constructs are useful as a part of the nucleic acid vaccination and chemotherapy regimen described in this application.

Potentiation of immune responses using anti-apoptotic proteins

Administration to a subject of a DNA vaccine and a chemotherapeutic drug may also be accompanied by administration of a nucleic acid encoding an anti-apoptotic protein, as described in WO2005/047501 and in U.S. Patent Application Publication No. 20070026076, both of which are incorporated by reference.

The present inventors have previously designed and disclosed an immunotherapeutic strategy that combines antigen-encoding DNA vaccine compositions with additional DNA vectors comprising anti-apoptotic genes including bcl-2, bc-lxL, XIAP, dominant negative mutants of caspase-8 and caspase-9, the products of which are known to inhibit apoptosis (Wu, *et al.* U.S. Patent Application Publication No.

20070026076, incorporated herein by reference). Serine protease inhibitor 6 (SPI-6) which inhibits granzyme B, may also be employed in compositions and methods to delay apoptotic cell death of DCs. The present inventors have shown that the harnessing of an additional biological mechanism, that of inhibiting apoptosis, significantly enhances T cell responses to DNA vaccines comprising antigen-coding sequences, as well as linked sequences encoding such IPPs.

Intradermal vaccination by gene gun efficiently delivers a DNA vaccine into DCs of the skin, resulting in the activation and priming of antigen-specific T cells in vivo. DCs, however, have a limited life span, hindering their long-term ability to prime antigen-specific T cells. According to the present invention, a strategy that combines combination therapy with methods to prolong the survival of DNA-transduced DCs enhances priming of antigen-specific T cells and thereby, increase DNA vaccine potency. Co-delivery of DNA encoding inhibitors of apoptosis (BCL-xL, BCL-2, XIAP, dominant negative caspase-9, or dominant negative caspase-8) with DNA encoding an antigen (exemplified as HPV-16 E7 protein) prolongs the survival of transduced DCs. More importantly, vaccinated subjects exhibited significant enhancement in antigen-specific CD8⁺ T cell immune responses, resulting in a potent antitumor effect against antigen-expressing tumors. Among these anti-apoptotic factors, BCL-XL demonstrated the greatest enhancement of both antigen-specific immune responses and antitumor effects. Thus, co-administration of a combination therapy including a DNA vaccine with one or more DNA constructs encoding anti-apoptotic proteins provides a way to enhance DNA vaccine potency.

Serine protease inhibitor 6 (SPI-6), also called Serpinb9, inhibits granzyme B, and may thereby delay apoptotic cell death in DCs. Intradermal co-administration of DNA encoding SPI-6 with DNA constructs encoding E7 linked to various IPPs significantly increased E7-specific CD8⁺ T cell and CD4⁺ Th1 cell responses and enhanced anti-tumor effects when compared to vaccination without SPI-6. Thus, in certain embodiments, combined methods are used that enhance MHC class I and II antigen processing with delivery of SPI-6 to potentiate immunity.

A similar approach employs DNA-based alphaviral RNA replicon vectors, also called suicidal DNA vectors. To enhance the immune response to an antigen, *e.g.*, HPV E7, a DNA-based Semliki Forest virus vector, pSCA1, the antigen DNA is fused with DNA encoding an anti-apoptotic polypeptide such BCL-xL, a member of the BCL-2 family. pSCA1 encoding a fusion protein of an antigen polypeptide and/BCL-xL delays cell death

in transfected DCs and generates significantly higher antigen-specific CD8⁺ T-cell-mediated immunity. The antiapoptotic function of BCL-xL is important for the enhancement of antigen-specific CD8⁺ T-cell responses. Thus, in one embodiment, delaying cell death induced by an otherwise desirable suicidal DNA vaccine enhances its
5 potency.

Thus, the present invention is also directed to combination therapies including administering a chemotherapeutic drug with a nucleic acid composition useful as an immunogen, comprising a combination of: (a) first nucleic acid vector comprising a first sequence encoding an antigenic polypeptide or peptide, which first vector optionally
10 comprises a second sequence linked to the first sequence, which second sequence encodes an immunogenicity-potentiating polypeptide (IPP); b) a second nucleic acid vector encoding an anti-apoptotic polypeptide, wherein, when the second vector is administered with the first vector to a subject, a T cell-mediated immune response to the antigenic polypeptide or peptide is induced that is greater in magnitude and/or duration than an
15 immune response induced by administration of the first vector alone. The first vector above may comprise a promoter operatively linked to the first and/or the second sequence.

In the above compositions the anti-apoptotic polypeptide may be selected from the group consisting of (a) BCL-xL, (b) BCL2, (c) XIAP, (d) FLICEc-s, (e) dominant-negative caspase-8, (f) dominant negative caspase-9, (g) SPI-6, and (h) a functional homologue or a
20 derivative of any of (a)-(g). The anti-apoptotic DNA may be physically linked to the antigen-encoding DNA. Examples of this are provided in U.S. Patent Application publication No. 20070026076, incorporated by reference, primarily in the form of suicidal DNA vaccine vectors. Alternatively, the anti-apoptotic DNA may be administered separately from, but in combination with the antigen-encoding DNA molecule. Even more
25 examples of the co-administration of these two types of vectors are provided in U.S. Patent Application No. 10/546,810 (publication number US 2007-0026076).

Exemplary nucleotide and amino acid sequences of anti-apoptotic and other proteins are provided in the sequence listing. Biologically active homologs of these proteins and constructs may also be used. Biologically active homologs is to be understood as described
30 herein in the context of other proteins, *e.g.*, IPPs.

The coding sequence for BCL-xL as present in the pcDNA3 vector of the present invention is SEQ ID NO:55; the amino acid sequence of BCL-xL is SEQ ID NO:56; the sequence pcDNA3-BCL-xL is SEQ ID NO:57 (the BCL-xL coding sequence corresponds

to nucleotides 983 to 1732); a pcDNA3 vector combining E7 and BCL-xL, designated pcDNA3-E7/BCL-xL is SEQ ID NO: 58 (the E7 and BCL-xL sequences correspond to nucleotides 960 to 2009); the amino acid sequence of the E7-BCL-xL chimeric or fusion polypeptide is SEQ ID NO: 59; a mutant BCL-xL ("mtBCL-xL") DNA sequence is SEQ ID NO: 60; the amino acid sequence of mtBCL-xL is SEQ ID NO: 61; the amino acid sequence of the E7-mtBCL-xL chimeric or fusion polypeptide is SEQ ID NO: 62; in the pcDNA-mtBCL-xL [SEQ ID NO: 63] vector, this mutant sequence is inserted in the same position that BCL-xL is inserted in SEQ ID NO: 57 and in the pcDNA-E7/mtBCL-xL [SEQ ID NO: 64], this sequence is inserted in the same position as the BCL-xL sequence is in SEQ ID NO: 58; the sequence of the suicidal DNA vector pSCA1-BCL-xL is SEQ ID NO: 65 (the BCL-xL sequence corresponds to nucleotides 7483 to 8232); the sequence of the "combined" vector, pSCA1-E7/BCL-xL is SEQ ID NO: 66 (the sequence of E7 and BCL-xL corresponds to nucleotides 7461 to 8510); the sequence of pSCA1-mtBCL-xL [SEQ ID NO: 67] is the same as that for the wild type BCL-xL except that the mtBCL-xL sequence is inserted in the same position as the wild type sequence in the pSCA1-mtBCL-xL vector; the sequence pSCA1-E7/mtBCL-xL [SEQ ID NO: 68] is the same as that for the wild type pSCA1-E7/BCL-xL above, except that the mtBCL-xL sequence is inserted in the same position as the wild type sequence; the sequence of the vector pSG5-BCL-xL is SEQ ID NO: 69 (the BCL-xL coding sequence corresponds to nucleotides 1061 to 1810); the sequence of the vector pSG5-mtBCL-xL is SEQ ID NO: 70 with the mutant BCL-xL sequence has the mtBCL-xL, shown above, inserted in the same location as for the wild type vector immediately above; the nucleotide sequence of the DNA encoding the XIAP anti-apoptotic protein is SEQ ID NO: 71; the amino acid of the vector comprising the XIAP anti-apoptotic protein coding sequence is SEQ ID NO: 72; the nucleotide sequence of the vector comprising the XIAP anti-apoptotic protein coding sequence, designated PSG5-XIAP is shown in SEQ ID NO: 73 (with the XIAP corresponding to nucleotides 1055 to 2553); the sequence of DNA encoding the anti-apoptotic protein FLICEc-s is SEQ ID NO: 74; the amino acid sequence of the anti-apoptotic protein FLICEc-s is SEQ ID NO: 75; the PSG5 vector encoding the anti-apoptotic protein FLICEc-s, designated PSG5-FLICEc-s, has the sequence SEQ ID NO: 76 (with the FLICEc-s sequence corresponding to nucleotides 1049 to 2443); the sequence of DNA encoding the anti-apoptotic protein Bcl2 is SEQ ID NO: 77; the amino acid sequence of Bcl2 is SEQ ID NO: 78; the PSG5 vector encoding Bcl2, designated PSG5-BCL2, has the sequence SEQ ID NO: 79 (with the Bcl2

sequence corresponding to nucleotides 1061 to 1678); the pSG5-dn-caspase-8 vector is SEQ ID NO: 80 (encoding the dominant-negative caspase-8 corresponding to nucleotides 1055 to 2449); the amino acid sequence of dn-caspase-8 is SEQ ID NO: 81; the pSG5-dn-caspase-9 vector is SEQ ID NO: 82 (encoding the dominant-negative caspase-9 as
 5 nucleotides 1055 to 2305); the amino acid sequence of dn-caspase-9 is SEQ ID NO: 83); the nucleotide sequence of murine serine protease inhibitor 6 (SPI-6, deposited in GENE BANK as NM 009256) is SEQ ID NO: 84; the amino acid sequence of the SPI-6 protein is SEQ ID NO: 85; the nucleic acid sequence of the mutant SPI-6 (mtSPI6) is SEQ ID NO: 86; the amino acid sequence of the mutant SPI-6 protein (mtSPI-6) is SEQ ID NO:
 10 87; the sequence of the pcDNA3-Spi6 vector is SEQ ID NO: 88 (the SPI-6 sequence corresponds to nucleotides 960 to 2081); and the sequence of the mutant vector pcDNA3-mtSpi6 vector [SEQ ID NO: 89] is the same as that above, except that the mtSPI-6 sequence is inserted in the same location in place of the wild type SPI-6.

Biologically active homologs of these nucleic acids and proteins may be used.
 15 Biologically active homologs are to be understood as described in the context of other proteins, *e.g.*, IPPs, herein. For example, a vector may encode an anti-apoptotic protein that is at least about 90%, 95%, 98% or 99% identical to that of a sequence set forth herein.

Oncolytic Viruses

20 Oncolytic viruses not only comprise a class of vectors able to encode and express a particular antigen to which an antigen-specific immune response is desired, but it also mediates killing of cancer cells. The term "oncolytic" and "oncolytic viruses" refer to cancer killing, *i.e.* "onco" meaning cancer and "lytic" meaning "killing". As used herein, where oncolytic refers to an "oncolytic virus" and an "OV," this virus represents a virus that
 25 may kill a cancer cell. In principle any virus capable of selective replication in neoplastic cells including cells of tumors, neoplasms, carcinomas, sarcomas, and the like may be utilized in the invention. Selective replication in neoplastic cells means that the virus replicates at least 1×10^4 , 1×10^5 , 1×10^6 , or more efficient in at least three cell lines established from different tumors compared to cells from at least three different non-
 30 tumorigenic tissues.

Oncolytic viruses may additionally or alternatively be targeted to specific tissues or tumor tissues. This can be achieved for example through transcriptional targeting of viral genes (*e.g.* WO 96/39841, incorporated by reference) or through modification of viral

proteins that are involved in the cellular binding and uptake mechanisms during the infection process (e.g. WO 2004033639 or WO 2003068809, all of which are incorporated by reference).

A wide range of viruses are contemplated as oncolytic viruses in the present invention, such as but not limited to herpes viruses, Adenovirus, Adeno-associated virus, influenza virus, reovirus, vesicular stomatitis virus (VSV), Newcastle virus, vaccinia virus, poliovirus, measles virus, mumps virus, sindbis virus (SrN) and sendai virus (SV). Tables 1-6 below provide an overview of examples previously published oncolytic viruses (taken from www.oncolyticVirus.org).

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TABLE 1

Oncolytic viruses targeting oncogenic ras or defective Interferon pathways.

Virus (Company, if known)	Viral gene defect	Cellular Target	Tumor models	References
Influenza A	NS1	PKR	Melanoma	(1)
HSV1mutants: R3616, 1716, G207 (Medigene, Inc.), MGH1	ICP34.5	Protein phosphatase 1a, Defective interferon signaling.	Brain, Colorectal, ovarian, lung, prostate, breast	(2, 3)
Reovirus (Oncolytics Biotech., Inc.)	None	Overactive Ras pathway	Brain, ovarian, breast, colorectal	(4-7).
VSV	None	Defective Interferon signaling	Melanoma	(8)
Newcastle disease virus (Provirus)	None	Overactive Ras pathway	Fibrosarcoma, Neuroblastoma	(9)

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TABLE 2

<u>Oncolytic viruses targeting defective p16 tumor suppressor pathways.</u>				
Virus (Company, if known)	Mutated viral gene	Cellular target	Effect	References
Adenovirus D24 and dl922-947 (Onyx Pharmaceuticals)	E1A-CR2 domain	PRB	Viral replication restricted to pRB-defective mutants	(10, 11)
Adenovirus CB106	E1A-CR1 and CR2 domains	PRB, p300, p107, p130	In keratinocytes, viral replication restricted to papillomavirus E6/E7 expressors	(12)
Adenovirus ONYX-411 (Onyx Pharmaceuticals)	a) E1A-CR1 b) E2F promoter driving E1A and E4 genes c) E3 deletion	PRB and upregulated E2F transcription factor	Increased dependence of virus replication on overactive E2F	(13)
HSV: hrR3, rRp450, HSV1yCD, MGH1, G207 Medigene, Inc.), G47Δ	UL39 (ICP6)	RR activity elevating dNTP pools	Viral replication depends on dNTP pools	(14, 15)
HSV Myb34.5 (Prestwick Scientific, Inc.)	a) UL39 (ICP6) b) B-Myb (E2F-responsive) promoter driving γ34.5 gene)	RR activity elevating dNTP pools and upregulated E2F transcription factor	Increased viral replicative dependence on E2F activity	(16, 17)
Vaccinia vvDD-GFP	TK gene	Elevated dTTP (due to cellular TK?)	Viral replication restricted to cells with dTTP pools	(18, 19)

TABLE 3

<u>Oncolytic viruses targeting defective p53 tumor suppressor pathway.</u>				
Virus (Company, if known)	Mutated viral gene	Cellular target	Effect	References
Adenovirus ONYX-015 (Onyx Pharmaceuticals)	E1B-55 Kd	p53	Viral replication restricted to p53-defective mutants	(20)
Adenovirus 01/PEME (Canji)	1) p53 promoter driving expression of E2F antagonist 2) E1A-CR1 p300 binding-domain 3) E3 deletion 4) Extra Major Late Promoter driving expression of E3-11.6 Kd	p53, p300.	Expression of E2 and subsequent viral genes dependent on loss of p53 function; wild-type p53 function enhanced by p300 coactivation; increased adenoviral release and cell death by adenoviral death protein (21)	(22)
AAV	AAV unusual DNA structure is precipitating factor	p53/p21	Lack of G2/M arrest in p53-defective cells, infected with AAV, causes cell death	(23)

TABLE 4

Targeting of oncolytic viruses with tumor-specific promoters.				
Virus (Company, if known)	Tumor-specific Promoter	Viral gene	Effect	References
Adenovirus CV706 (Calydon, Inc.)	PSA (prostate)	E1A	Replication restricted to prostate tissue	(24)
Adenovirus CN787 (Calydon, Inc.)	a) Rat probasin promoter for E1A b) PSA for E1B	E1A and E1B	Same as above	(25, 26)
Adenovirus CV980 (Calydon, Inc.)	AFP (hepatocellular carcinoma)	E1A and E1B	Replication restricted to hepatic tumors.	(27)
Adenovirus ONYX-411 (Onyx Pharmaceuticals)	E2F1 promoter (most tumors)	E1A and E4	Increased dependence of virus replication on overactive E2F	(13)
Adenovirus 01/PEME (Canji Inc.)	p53 promoter (most tumors)	E2F antagonist.	Expression of E2 and subsequent viral genes dependent on loss of p53 function	(22)
CG8840 (Cell Genesys, Inc.)	Uroplakin II (bladder)	E1A and E1B	Replication restricted to bladder cancer	(28)
KD1-SPB	Surfactant protein B	E4	Replication improved in lung tumors	(29)
HSV Myb34.5 (Prestwick Scientific, Inc.)	B-Myb promoter (most tumors)	g34.5 (ICP34.5)	Improved replication in tumors	(16, 17)
HSV DF3g34.5	DF3 promoter	g34.5 (ICP34.5)	Improved replication in MUC1-positive pancreatic and breast tumor cells.	(30)
HSV G92A	Albumin promoter	ICP4	Replication restricted in hepatoma	(31)

TABLE 5

Targeting with "tumor-selective" infection.				
Virus	Redirected viral ligand	Cellular target	Effect	References
Dual Adenovirus system: AdsCAR-EGF + $\Delta 24$	Bispecific-antibody binding adenovirus fiber to EGFR	EGFR	Redirects viral infection to EGFR-expressing cells	(32)
Adenovirus: Ad5-D24RGD	H1-loop in Fiber of Ad modified by incorporation of RGD	Integrin	Redirects viral infection to integrin-expressing cells.	(33)
D24 or ONYX-015	Infusion of bispecific antibodies to fiber and EGFR	EGFR	Redirects viral infection to EGFR-expressing cells	(34)
Ad 5/35	Fiber of adenovirus serotype 35 substituted into adenovirus serotype 5	Unknown	Redirects viral infection away from CAR and towards an unidentified cellular receptor present in human breast cancer	(35)

TABLE 6

<u>Other mechanisms of oncolytic virus targeting.</u>					
Virus	Defect in viral gene		Effect	Oncolytic mechanism	References
Vaccinia vvDD-GFP	Vaccinia Growth Factor		Cannot prime neighboring cells to divide	Only dividing tumor cells will replicate, because normal cells are not “primed” by VGF	(18)
Poliovirus PV1(RIPO)	Substitutes poliovirus IRES element with rhinovirus 2		Loss of neurovirulence, because neurons cannot translate	Tumor cells can still propagate virus	(36)
HSV1: rRp450	ICP6	CYP2B1	Cyclophosphamide > Phosphoramide Mustard	Predominant anticancer action + immunosuppressive effects.	(15)
Adenovirus: FGR	E1B55kD	Fused TK-CD gene	Ganciclovir > GCV-Phosphate + 5-fluorocytosine > 5fluorouracil	Combination of FGR, GCV, 5FC and radiation shows predominant anticancer action	(50)
HSV1: Fu-10	Unknown	Fusogenic glycol-protein	Not applicable	Enhanced fusion of cell membranes caused by replicating virus increases anticancer effect	(51)
Adenovirus: ad5/IFN	E3	Interferon	Not applicable	Increased anticancer effect compared to control E3-deleted adenovirus	(52)
Adenovirus: Ad.TK ^{RC} , Ad.OW34	E1B55KD	TK	Ganciclovir > GCV-Phosphate	Contradictory anticancer effects	(53, 54)
Adenovirus: Ig.Ad5E1*.E3TK	E3-19K	TK	Ganciclovir > GCV-Phosphate	Increased anticancer effect in glioma	(55)
HSV1: Mix of G207 + Defective HSV-IL2	ICP6 and ICP34.5	IL2	Not applicable	At low dose, the mix was more effective than either virus alone	(56) ¹⁰
HSV1: NV1042	Complex	IL12	Not applicable	Increased anticancer effect	(57)
HSV1: Mix of G207 + Defective HSV-soluble B7-1	ICP6 and ICP34.5	Soluble B7-1	Not applicable	Increased anticancer effect	(58)
HSV1: HSV1yCD	ICP6	Yeast cytosine deaminase	5-fluorocytosine > 5-fluorouracil	Increased anticancer effect minimal antiviral effect	(59) ²⁰
Vaccinia: VCD	TK	Bacterial cytosine deaminase	5-fluorocytosine > 5-fluorouracil	Increased effect at low viral dose	(60)
HSV1	ICP34.5	IL4, IL12, IL10	Not applicable	Increased anticancer effect for IL12 and IL4, but antagonistic effect for IL10	(61, 62)

TABLE 7

<u>Oncolytic viruses that express anti-cancer cDNAs.</u>					
Virus	Viral gene defect	Anticancer cDNA	Prodrug > Metabolite	Effect	Reference
HSV1: hrR3, MGH1, G207 (Medigene, Inc.)	ICP6 and/or ICP34.5	TK	Ganciclovir > GCV-Phosphate	Predominant anticancer action in some situations, but increased antiviral action in others (FIG. 5)	(42-49)

Methods for producing and purifying the oncolytic virus used according to the invention are described in the publications cited below.

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Generally, the virus may be purified to render it essentially free of undesirable
 10 contaminants, such as defective interfering viral particles or endotoxins and other pyrogens,
 so that it will not cause any undesired reactions in the cell, animal, or individual receiving
 the virus. A means of purifying the virus involves the use of buoyant density gradients,
 such as cesium chloride gradient centrifugation.

In one embodiment, the oncolytic virus, e.g. vaccinia virus, further contains foreign
 15 DNA, i.e., DNA which is not derived from said virus. This DNA may encode the antigen to
 which an antigen-specific immune response is desired.

In other embodiments, the foreign DNA may be a heterologous promoter region, a
 structural gene, or a promoter operatively linked to such a gene. Representative promoters
 include, but are not limited to, the CMV promoter, LacZ promoter, Egr promoter or known
 20 HSV promoters. In a one embodiment, the structural gene is selected from the group of a
 cytokine/chemokine, a suicide gene, a fusogenic protein or a marker gene.
 Cytokines/chemokines that may be used include, but are not limited to, IL-4, IL-12 and
 GM-CSF. Suicide genes that may be used include, but are not limited to, p450 and cytosine
 deaminase. A fusogenic protein is for example Gibbon ape leukemia virus envelope.
 25 Common marker genes are luciferase, GFP or one of its variants, and LacZ.

In a further embodiment the oncolytic virus is further modified to have an altered
 host cell specificity. Such mutants are for example known for HSV-1 from WO
 2004/033639, incorporated by reference, US 2005271620 included by reference, Kamiyama
et al. (2006) and Menotti *et al.* (2006). Here, glycoproteins of HSV-1 such as gD, gC are
 30 fused to a ligand, especially to single-chain antibodies, that specifically bind to target cells
 of choice. Further, to detarget such viruses from their natural receptors and heparin sulfate
 proteoglycan deletions and/or point mutations are made in gB, gC and/or gD (WO
 2004/033639, incorporated by reference, Zhou and Roizman, 2006).

Chemotherapeutic drugs

Drugs may also further be administered to a mammal in accordance with the methods and compositions taught herein. Generally, any drug that reduces the growth of cells without significantly affecting the immune system may be used, or at least not suppressing the immune system to the extent of eliminating the positive effects of a DNA vaccine that is administered to the subject. In one embodiment, the drugs are chemotherapeutic drugs.

A wide variety of chemotherapeutic drugs may be used, provided that the drug stimulates the effect of a vaccine, *e.g.*, DNA vaccine. In certain embodiments, a chemotherapeutic drug may be a drug that (a) induces apoptosis of cells, in particular, cancer cells, when contacted therewith; (b) reduces tumor burden; and/or (c) enhances CD8⁺ T cell-mediated antitumor immunity. In certain embodiments, the drug must also be one that does not inhibit the immune system, or at least not at certain concentrations.

In one embodiment, the chemotherapeutic drug is epigallocatechin-3-gallate (EGCG) or a chemical derivative or pharmaceutically acceptable salt thereof. Epigallocatechin gallate (EGCG) is the major polyphenol component found in green tea. EGCG has demonstrated antitumor effects in various human and animal models, including cancers of the breast, prostate, stomach, esophagus, colon, pancreas, skin, lung, and other sites. EGCG has been shown to act on different pathways to regulate cancer cell growth, survival, angiogenesis and metastasis. For example, some studies suggest that EGCG protects against cancer by causing cell cycle arrest and inducing apoptosis. It is also reported that telomerase inhibition might be one of the major mechanisms underlying the anticancer effects of EGCG. In comparison with commonly-used antitumor agents, including retinoids and doxorubicin, EGCG has a relatively low toxicity and is convenient to administer due to its oral bioavailability. Thus, EGCG has been used in clinical trials and appears to be a potentially ideal antitumor agent.

Exemplary analogs or derivatives of EGCG include (-)-EGCG, (+)-EGCG, (-)-EGCG-amide, (-)-GCG, (+)-GCG, (+)-EGCG-amide, (-)-ECG, (-)-CG, genistein, GTP-1, GTP-2, GTP-3, GTP-4, GTP-5, Bn-(+)-epigallocatechin gallate (US 2004/0186167, incorporated by reference), and dideoxy-epigallocatechin gallate (Furuta, *et al.*, Bioorg. Med. Chem. Letters, 2007, 11: 3095-3098). For additional examples, see US 2004/0186167 (incorporated by reference in its entirety); Waleh, *et al.*, Anticancer Res., 2005, 25: 397-402; Wai, *et al.*, Bioorg. Med. Chem., 2004, 12: 5587-5593; Smith, *et al.*,

Proteins: Struc. Func. & Bioinform., 2003, 54: 58-70; US 7,109,236 (incorporated by reference in its entirety); Landis-Piwowar, *et al.*, Int. J. Mol. Med., 2005, 15: 735-742; Landis-Piwowar, *et al.*, J. Cell. Phys., 2007, 213: 252-260; Daniel, *et al.*, Int. J. Mol. Med., 2006, 18: 625-632; Tanaka, *et al.*, Ang. Chemie Int., 2007, 46: 5934-5937.

5 Another chemotherapeutic drug that may be used is (a) 5,6 di-methylxanthenone-4-acetic acid (DMXAA), or a chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include xanthenone-4-acetic acid, flavone-8-acetic acid, xanthen-9-one-4-acetic acid, methyl (2,2-dimethyl-6-oxo-1,2-dihydro-6H-3,11-dioxacyclopenta[α]anthracen-10-yl)acetate, methyl (2-methyl-6-oxo-1,2-dihydro-6H-3,11-dioxacyclopenta[α]anthracen-10-yl)acetate, methyl (3,3-dimethyl-7-oxo-3H,7H-4,12-dioxabenz[α]anthracen-10-yl)acetate, methyl-6-alkyloxyxanthen-9-one-4-acetates (Gobbi, *et al.*, 2002, J. Med. Chem., 45: 4931) or a . For additional examples, see WO 2007/023302 A1, WO 2007/023307 A1, US 2006/9505, WO 2004/39363 A1, WO 2003/80044 A1, AU 2003/217035 A1, and AU 2003/282215 A1, each incorporated by
15 reference in their entirety.

A chemotherapeutic drug may also be cisplatin, or a chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include dichloro[4,4'-bis(4,4,4-trifluorobutyl)-2,2'-bipyridine]platinum (Kyler *et al.*, Bioorganic & Medicinal Chemistry, 2006, 14: 8692-8700), cis-[Rh2(-
20 O2CCH3)2(CH3CN)6]2+ (Lutterman *et al.*, J. Am. Chem. Soc., 2006, 128: 738 -739), (+)-cis-(1,1-Cyclobutanedicarboxylato)((2R)-2-methyl-1,4-butanediamine-N,N')platinum (O'Brien *et al.*, Cancer Res., 1992, 52: 4130-4134), cis-bisneodecanoato-trans-R,R-1,2-diaminocyclohexane platinum(II) (Lu *et al.*, J. of Clin. Oncol., 2005, 23: 3495-3501), carboplatin (Woloschuk, Drug Intell. Clin. Pharm., 1988, 22: 843-849), seabriplatin
25 (Kanazawa *et al.*, Head & Neck, 2006, 14: 38-43), satraplatin (Amorino *et al.*, Cancer Chemother. and Pharmacol., 2000, 46: 423-426), azane (dichloroplatinum) (CID: 11961987), azanide (CID: 6712951), platinol (CID: 5702198), lopac-P-4394 (CID: 5460033), MOLI001226 (CID: 450696), trichloroplatinum (CID: 420479), platinate(1-), amminetrichloro-, ammonium (CID: 160995), triammineplatinum (CID: 119232),
30 biocisplatinum (CID: 84691), platiblastin (CID: 2767) and pharmaceutically acceptable salts thereof. For additional examples, see US 5922689, US 4996337, US 4937358, US 4808730, US 6130245, US 7232919, and US 7038071, each incorporated by reference in their entirety.

Another chemotherapeutic drug that may be used is apigenin, or a chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include acacetin, chrysin, kampherol, luteolin, myricetin, naringenin, quercetin (Wang *et al.*, Nutrition and Cancer, 2004, 48: 106-114), puerarin (US 5 2006/0276458, incorporated by reference in its entirety) and pharmaceutically acceptable salts thereof. For additional examples, see US 2006/189680 A1, incorporated by reference in its entirety).

Another chemotherapeutic drug that may be used is doxorubicin, or a chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary 10 analogs or derivatives include anthracyclines, 3'-deamino-3'-(3-cyano-4-morpholinyl)doxorubicin, WP744 (Faderl, *et al.*, Cancer Res., 2001, 21: 3777-3784), annamycin (Zou, *et al.*, Cancer Chemother. Pharmacol., 1993, 32:190-196), 5-imino-daunorubicin, 2-pyrrolinodoxorubicin, DA-125 (Lim, *et al.*, Cancer Chemother. Pharmacol., 1997, 40: 23-30), 4-demethoxy-4'-O-methyldoxorubicin, PNU 152243 and 15 pharmaceutically acceptable salts thereof (Yuan, *et al.*, Anti-Cancer Drugs, 2004, 15: 641-646). For additional examples, see EP 1242438 B1, US 6630579, AU 2001/29066 B2, US 4826964, US 4672057, US 4314054, AU 2002/358298 A1, and US 4301277, each incorporated by reference in their entirety);

Other chemotherapeutic drugs that may be used are anti-death receptor 5 antibodies 20 and binding proteins, and their derivatives, including antibody fragments, single-chain antibodies (scFvs), Avimers, chimeric antibodies, humanized antibodies, human antibodies and peptides binding death receptor 5. For examples, see US 2007/31414 and US 2006/269554, each incorporated by reference in their entirety.

Another chemotherapeutic drug that may be used is bortezomib, or a chemical 25 derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include MLN-273 and pharmaceutically acceptable salts thereof (Witola, *et al.*, Eukaryotic Cell, 2007, doi:10.1128/EC.00229-07). For additional possibilities, see Groll, *et al.*, Structure, 14:451.

Another chemotherapeutic drug that may be used is 5-aza-2-deoxycytidine, or a 30 chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include other deoxycytidine derivatives and other nucleotide derivatives, such as deoxyadenine derivatives, deoxyguanine derivatives, deoxythymidine derivatives and pharmaceutically acceptable salts thereof.

Another chemotherapeutic drug that may be used is genistein, or a chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include 7-O-modified genistein derivatives (Zhang, *et al.*, Chem. & Biodiv., 2007, 4: 248-255), 4',5,7-tri[3-(2-hydroxyethylthio)propoxy]isoflavone, genistein glycosides (Polkowski, Cancer Letters, 2004, 203: 59-69), other genistein derivatives (Li, *et al.*, Chem & Biodiv., 2006, 4: 463-472; Sarkar, *et al.*, Mini. Rev. Med. Chem., 2006, 6: 401-407) or pharmaceutically acceptable salts thereof. For additional examples, see US 6541613, US 6958156, and WO/2002/081491, each incorporated by reference in their entirety.

Another chemotherapeutic drug that may be used is celecoxib, or a chemical derivative or analog thereof or a pharmaceutically acceptable salt thereof. Exemplary analogs or derivatives include N-(2-aminoethyl)-4-[5-(4-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 4-[5-(4-aminophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, OSU03012 (Johnson, *et al.*, Blood, 2005, 105: 2504-2509), OSU03013 (Tong, *et al.*, Lung Cancer, 2006, 52: 117-124), dimethyl celecoxib (Backhus, *et al.*, J. Thorac. and Cardiovasc. Surg., 2005, 130: 1406-1412), and other derivatives or pharmaceutically acceptable salts thereof (Ding, *et al.*, Int. J. Cancer, 2005, 113: 803-810; Zhu, *et al.*, Cancer Res., 2004, 64: 4309-4318; Song, *et al.*, J. Natl. Cancer Inst., 2002, 94: 585-591). For additional examples, see US 7026346, incorporated by reference in its entirety.

One of skill in the art will readily recognize that other chemotherapeutics can be used with the methods and kits disclosed in the present invention, including proteasome inhibitors (in addition to bortezomib) and inhibitors of DNA methylation. Other drugs that may be used include Paclitaxel; selenium compounds; SN38, etoposide, 5-Fluorouracil; VP-16, cox-2 inhibitors, Vioxx, cyclooxygenase-2 inhibitors, curcumin, MPC-6827, tamoxifen or flutamide, etoposide, PG490, 2-methoxyestradiol, AEE-788, aglycon protopanaxadiol, aplidine, ARQ-501, arsenic trioxide, BMS-387032, canertinib dihydrochloride, canfosfamide hydrochloride, combretastatin A-4 prodrug, idronoxil, indisulam, INGN-201, mapatumumab, motexafin gadolinium, oblimersen sodium, OGX-011, patupilone, PXD-101, rubitecan, tipifarnib, trabectedin PXD-101, methotrexate, Zerumbone, camptothecin, MG-98, VX-680, Ceflatonin, Oblimersen sodium, motexafin gadolinium, 1D09C3, PCK-3145, ME-2 and apoptosis-inducing-ligand (TRAIL/Apo-2 ligand). Others are provided in a report entitled "competitive outlook on apoptosis in

oncology, Dec. 2006, published by Bioseeker, and available, *e.g.*, at http://bizwiz.bioseeker.com/bw/Archives/Files/TOC_BSG0612193.pdf.

Generally, any drug that affects an apoptosis target may also be used. Apoptosis targets include the tumour-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors, the BCL2 family of anti-apoptotic proteins (such as Bcl-2), inhibitor of apoptosis (IAP) proteins, MDM2, p53, TRAIL and caspases. Exemplary targets include B-cell CLL/lymphoma 2, Caspase 3, CD4 molecule, Cytosolic ovarian carcinoma antigen 1, Eukaryotic translation elongation factor 2, Farnesyltransferase, CAAX box, alpha; Fc fragment of IgE; Histone deacetylase 1; Histone deacetylase 2; Interleukin 13 receptor, alpha 1; Phosphodiesterase 2A, cGMP-stimulated Phosphodiesterase 5A, cGMP-specific; Protein kinase C, beta 1; Steroid 5-alpha-reductase, alpha polypeptide 1; 8.1.15 Topoisomerase (DNA) I; Topoisomerase (DNA) II alpha; Tubulin, beta polypeptide; and p53 protein.

In certain embodiments, the compounds described herein, *e.g.*, EGCG, are naturally-occurring and may, *e.g.*, be isolated from nature. Accordingly, in certain embodiments, a compound is used in an isolated or purified form, *i.e.*, it is not in a form in which it is naturally occurring. For example, an isolated compound may contain less than about 50%, 30%, 10%, 1%, 0.1% or 0.01% of a molecule that is associated with the compound in nature. A purified preparation of a compound may comprise at least about 50%, 70%, 80%, 90%, 95%, 97%, 98% or 99% of the compound, by molecule number or by weight. Compositions may comprise, consist essentially of consist of one or more compounds described herein. Some compounds that are naturally occurring may also be synthesized in a laboratory and may be referred to as "synthetic." Yet other compounds described herein are non-naturally occurring.

In certain embodiments, the chemotherapeutic drug is in a preparation from a natural source, *e.g.*, a preparation from green tea.

Pharmaceutical compositions comprising 1, 2, 3, 4, 5 or more chemotherapeutic drugs or pharmaceutically acceptable salts thereof are also provided herein. A pharmaceutical composition may comprise a pharmaceutically acceptable carrier. A composition, *e.g.*, a pharmaceutical composition, may also comprise a vaccine, *e.g.*, a DNA vaccine, and optionally 1, 2, 3, 4, 5 or more vectors, *e.g.*, other DNA vaccines or other constructs, *e.g.*, described herein.

Compounds may be provided with a pharmaceutically acceptable salt. The term “pharmaceutically acceptable salts” is art-recognized, and includes relatively non-toxic, inorganic and organic acid addition salts of compositions, including without limitation, therapeutic agents, excipients, other materials and the like. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric acid and sulfuric acid, and those derived from organic acids, such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like. Examples of suitable inorganic bases for the formation of salts include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc and the like.

Salts may also be formed with suitable organic bases, including those that are non-toxic and strong enough to form such salts. For purposes of illustration, the class of such organic bases may include mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and triethylamine; mono-, di- or trihydroxyalkylamines such as mono-, di-, and triethanolamine; amino acids, such as arginine and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; (trihydroxymethyl)aminoethane; and the like. See, for example, *J. Pharm. Sci.*, 66:1-19 (1977).

Also provided herein are compositions and kits comprising one or more DNA vaccines and one or more chemotherapeutic drugs, and optionally one or more other constructs described herein.

Therapeutic compositions and their administration

A vaccine composition comprising a nucleic acid, a particle comprising the nucleic acid or a cell expressing this nucleic acid, may be administered to a mammalian subject.

The vaccine composition may be administered in a pharmaceutically acceptable carrier in a biologically-effective and/or a therapeutically-effective amount.

Certain conditions as described herein are disclosed in the Examples. The composition may be given alone or in combination with another protein or peptide such as an immunostimulatory molecule. Treatment may include administration of an adjuvant, used in its broadest sense to include any nonspecific immune stimulating compound such as an interferon. Adjuvants contemplated herein include resorcinols, non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecyl polyethylene ether.

A therapeutically effective amount is a dosage that, when given for an effective period of time, achieves the desired immunological or clinical effect.

A therapeutically active amount of a nucleic acid encoding the fusion polypeptide may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the peptide to elicit a desired response in the individual. Dosage regimes may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A therapeutically effective amount of the protein, in cell associated form may be stated in terms of the protein or cell equivalents.

Thus an effective amount of the vaccine may be between about 1 nanogram and about 1 gram per kilogram of body weight of the recipient, between about 0.1 $\mu\text{g/kg}$ and about 10mg/kg, between about 1 $\mu\text{g/kg}$ and about 1 mg/kg. Dosage forms suitable for internal administration may contain (for the latter dose range) from about 0.1 μg to 100 μg of active ingredient per unit. The active ingredient may vary from 0.5 to 95% by weight based on the total weight of the composition. Alternatively, an effective dose of cells transfected with the DNA vaccine constructs of the present invention is between about 10^4 and 10^8 cells. Those skilled in the art of immunotherapy will be able to adjust these doses without undue experimentation.

In certain embodiments, the routes of administration of the DNA may include (a) intratumoral, peritumoral, and/or intradermal “gene gun” delivery wherein DNA-coated gold particles in an effective amount are delivered using a helium-driven gene gun (BioRad, Hercules, CA) with a discharge pressure set at a known level, *e.g.*, of 400 p.s.i.; (b) intramuscularly (i.m.) injection using a conventional syringe needle; and (c) use of a needle-free biojector such as the Biojector 2000 (Bioject Inc., Portland, OR) which is an injection device consisting of an injector and a disposable syringe. The orifice size controls the depth of penetration. For example, 50 μg of DNA may be delivered using the Biojector with no. 2 syringe nozzle.

Other routes of administration include the following. The term “systemic administration” refers to administration of a composition or agent such as a DNA vaccine as described herein, in a manner that results in the introduction of the composition into the subject’s circulatory system or otherwise permits its spread throughout the body. “Regional” administration refers to administration into a specific, and somewhat more

limited, anatomical space, such as intraperitoneal, intrathecal, subdural, or to a specific organ. "Local administration" refers to administration of a composition or drug into a limited, or circumscribed, anatomic space, such as intratumoral injection into a tumor mass, subcutaneous injections, intradermal or intramuscular injections. Those of skill in the art will understand that local administration or regional administration may also result in entry of a composition into the circulatory system i.e., rendering it systemic to one degree or another. Other routes of administration include oral, intranasal or rectal or any other route known in the art.

For accomplishing the objectives of the present invention, nucleic acid therapy may be accomplished by direct transfer of a functionally active DNA into mammalian somatic tissue or organ *in vivo*. DNA transfer can be achieved using a number of approaches described below. These systems can be tested for successful expression *in vitro* by use of a selectable marker (*e.g.*, G418 resistance) to select transfected clones expressing the DNA, followed by detection of the presence of the antigen-containing expression product (after treatment with the inducer in the case of an inducible system) using an antibody to the product in an appropriate immunoassay.

The DNA molecules, *e.g.*, encoding a fusion polypeptides, may also be packaged into retrovirus vectors using packaging cell lines that produce replication-defective retroviruses, as is well-known in the art (*e.g.*, Cone, R.D. *et al.*, *Proc Natl Acad Sci USA* 81:6349-53, 1984; Mann, RF *et al.*, *Cell* 33:153-9, 1983; Miller, AD *et al.*, *Molec Cell Biol* 5:431-7, 1985; Sorge, J, *et al.*, *Molec Cell Biol* 4:1730-7, 1984; Hock, RA *et al.*, *Nature* 320:257, 1986; Miller, AD *et al.*, *Molec Cell Biol* 6:2895-2902 (1986). Newer packaging cell lines which are efficient and safe for gene transfer have also been described (Bank *et al.*, US Pat. 5,278,056, incorporated by reference).

The above approach can be utilized in a site specific manner to deliver the retroviral vector to the tissue or organ of choice. Thus, for example, a catheter delivery system can be used (Nabel, EG *et al.*, *Science* 244:1342 (1989)). Such methods, using either a retroviral vector or a liposome vector, are particularly useful to deliver the nucleic acid to be expressed to a blood vessel wall, or into the blood circulation of a tumor.

Depending on the route of administration, the composition may be coated in a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the compound. Thus it may be necessary to coat the composition with, or co-administer the composition with, a material to prevent its

inactivation. For example, an enzyme inhibitors of nucleases or proteases (*e.g.*, pancreatic trypsin inhibitor, diisopropylfluorophosphate and trasylol) or in an appropriate carrier such as liposomes (including water-in-oil-in-water emulsions as well as conventional liposomes (Strejan *et al.*, *J. Neuroimmunol* 7:27, 1984).

5 Other pharmaceutically acceptable carriers for the nucleic acid vaccine compositions according to the present invention are liposomes, pharmaceutical compositions in which the active protein is contained either dispersed or variously present in corpuscles consisting of aqueous concentric layers adherent to lipidic layers. The active protein may be present in the aqueous layer and in the lipidic layer, inside or outside, or, in
10 any event, in the non-homogeneous system generally known as a liposomic suspension. The hydrophobic layer, or lipidic layer, generally, but not exclusively, comprises phospholipids such as lecithin and sphingomyelin, steroids such as cholesterol, more or less ionic surface active substances such as dicetylphosphate, stearylamine or phosphatidic acid, and/or other materials of a hydrophobic nature. Those skilled in the art will appreciate
15 other suitable embodiments of the present liposomal formulations.

A chemotherapeutic drug may be administered in doses that are similar to the doses that the chemotherapeutic drug is used to be administered for cancer therapy. Alternatively, it may be possible to use lower doses, *e.g.*, doses that are lower by 10%, 30%, 50%, or 2, 5, or 10 fold lower. Generally, the dose of chemotherapeutic agent is a
20 dose that is effective to increase the effectiveness of a DNA vaccine, but less than a dose that results in significant immunosuppression or immunosuppression that essentially cancels out the effect of the DNA vaccine.

The route of administration of chemotherapeutic drugs may depend on the drug. For use in the methods described herein, a chemotherapeutic drug may be used as it is
25 commonly used in known methods. Generally, the drugs will be administered orally or they may be injected. The regimen of administration of the drugs may be the same as it is commonly used in known methods. For example, certain drugs are administered one time, other drugs are administered every third day for a set period of time, yet other drugs are administered every other day or every third, fourth, fifth, sixth day or weekly. The
30 Examples provide exemplary regimens for administrating the drugs, as well as DNA vaccines.

The compositions of the present invention, may be administered simultaneously or subsequently. When administered simultaneously, the different components may be

administered as one composition. Accordingly, also provided herein are compositions, *e.g.*, pharmaceutical compositions comprising one or more agents.

In one embodiment, a subject first receives one or more doses of chemotherapeutic drug and then one or more doses of DNA vaccine. In the case of DMXAA, it may be
5 preferable to administer to the subject a dose of DNA vaccine first and then a dose of chemotherapeutic drug. One may administer 1, 2, 3, 4, 5 or more doses of DNA vaccine and 1, 2, 3, 4, 5 or more doses of chemotherapeutic agent.

A method may further comprise subjecting a subject to another cancer treatment, *e.g.*, radiotherapy, an anti-angiogenesis agent and/or a hydrogel-based system.

10 As used herein "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. 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 therapeutic compositions is
15 contemplated. Supplementary active compounds can also be incorporated into the compositions.

Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Pharmaceutical compositions suitable for injection include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of
20 sterile injectable solutions or dispersion. Isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride may be included in the pharmaceutical composition. In all cases, the composition should be sterile and should be fluid. It should be stable under the conditions of manufacture and storage and must include preservatives that prevent contamination with microorganisms such as bacteria and fungi. Dispersions
25 can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

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
30 example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

Prevention of the action of microorganisms in the pharmaceutical composition can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like.

Compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for a mammalian subject; each unit contains a predetermined quantity of active material (*e.g.*, the nucleic acid vaccine) 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 (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of, and sensitivity of, individual subjects.

For lung instillation, aerosolized solutions are used. In a sprayable aerosol preparations, the active protein may be in combination with a solid or liquid inert carrier material. This may also be packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant. The aerosol preparations can contain solvents, buffers, surfactants, and antioxidants in addition to the protein of the invention.

Diseases that may be treated as described herein include hyper proliferative diseases, *e.g.*, cancer, whether localized or having metastasized. Exemplary cancers include head and neck cancers and cervical cancer. Any cancer can be treated provided that there is a tumor associated antigen that is associated with the particular cancer. Other cancers include skin cancer, lung cancer, colon cancer, kidney cancer, breast cancer, prostate cancer, pancreatic cancer, bone cancer, brain cancer, as well as blood cancers, *e.g.*, myeloma, leukemia and lymphoma. Generally, any cell growth can be treated provided that there is an antigen associated with the cell growth, which antigen or homolog thereof can be encoded by a DNA vaccine.

Treating a subject includes curing a subject or improving at least one symptom of the disease or preventing or reducing the likelihood of the disease to return. For example, treating a subject having cancer could be reducing the tumor mass of a subject, *e.g.*, by about 10%, 30%, 50%, 75%, 90% or more, eliminating the tumor, preventing or reducing the likelihood of the tumor to return, or partial or complete remission.

All references cited herein are all incorporated by reference herein, in their entirety, whether specifically incorporated or not. All publications, patents, patent applications,

GenBank sequences and ATCC deposits, cited herein are hereby expressly incorporated by reference for all purposes. In particular, all nucleotide sequences, amino acid sequences, nucleic constructs, DNA vaccines, methods of administration, particular orders of administration of DNA vaccines and agents that are described in the patents, patent applications and other publications referred to herein or authored by one or more of the inventors of this application are specifically incorporated by reference herein. In case of conflict, the definitions within the instant application govern.

Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the invention and without undue experimentation.

The present description is further illustrated by the following examples, which should not be construed as limiting in any way.

15 **EXAMPLES**

Example 1: Material and Methods For Examples 2-6

A. Mice

Female C57BL/6 mice (H-2K^b and I-A^b), 5 to 6 weeks of age, were purchased from National Cancer Institute (Frederick, MD). Transgenic mice, OT-1, that express TCR specific for ovalbumin peptide, SIINFEKL, were purchased from The Jackson Laboratory. All of the mice were maintained under specific pathogen-free conditions in the animal facility at Johns Hopkins Hospital (Baltimore, MD). Animals were used in compliance with institutional animal health care regulations, and all animal experimental procedures were approved by the Johns Hopkins Institutional Animal Care and Use Committee.

B. Cell lines

The production and maintenance of TC-1 cells or TC-1-luciferase transduced (TC-1 luc) cells have been described previously (Lin *et al.*, Cancer. Res., 56:21-6 (1996); Kim *et al.*, Human Gene Ther., 18:575-88 (2007)). Mouse melanoma cell B16/F10 and thymoma cells EL4 (H-2^b) were purchased from ATCC (Rockville, MD, USA). For the generation of CTLs specific for H-2K^b-OVA, 1x10⁷ EG7 cells (EL4 cells transfected with ovalbumin cDNA) were irradiated (10,000 rad) and cultured for 6 days in complete RPMI-1640 medium with 1x10⁷ spleen cells from OT-1 mice. All cell lines were grown in RPMI-1640,

supplemented with 10% (v/v) fetal bovine serum, 50 U/ml penicillin/streptomycin, 2 mM L-glutamine, 1 mM sodium pyruvate, 2 mM nonessential amino acids, and 0.4 mg/ml G418 at 37°C with 5% CO₂.

5 C. Plasmid DNA constructs

The generation of recombinant plasmid pcDNA3 encoding CRT/E7 (p-CRT/E7) or recombinant pcDNA3 encoding ovalbumin (p-OVA) has been described previously (Kim *et al.*, J. Clin. Invest, 112:109-17 (2003); Peng *et al.*, J. Biomed. Sci., 12:689-700 (2005)). The accuracy of the DNA construct was confirmed by DNA sequencing. For the gene gun-mediated intradermal vaccination, 2 µg/mouse of recombinant plasmid DNA were delivered to the shaved abdominal region of C57BL/6 mice using a helium-driven gene gun (BioRad, Hercules, CA, USA) with a discharge pressure of 400 p.s.i., according to a previously described protocol (Chen *et al.*, Cancer Res., 60:1035-42 (2000)).

15 D. Recombinant vaccinia viruses

The wild type vaccinia virus (Vac-WT) was prepared as described previously (Wu *et al.*, Proc. Natl. Acad. Sci. U S A, 92:11671-5 (1995)). The luciferase-expressing vaccinia virus (Vac-luc) was generated using a previously described protocol. It contains two reporter genes (luc and lacZ) inserted into the thymidine kinase region of VV (tk-) as described (Chen *et al.*, J. Immunotherapy, 24:46-57 (2001)). The vaccinia virus expressing the full-length chicken OVA (Vac-OVA) was generated using a previously described protocol (Norbury *et al.*, J. Immunol., 166:4355-62 (2001)). The generation of recombinant vaccinia virus encoding calreticulin (CRT) linked to a model tumor antigen HPV-16 E7 (Vac-CRT/E7) was performed using a protocol similar to what has been described earlier (Earl *et al.*, AIDS Res. Hum. Retroviruses, 9:589-94 (1993)). The generation of recombinant vaccinia virus expressing green fluorescent protein (Vac-GFP) was performed using a protocol similar to what has been described earlier (Ward *et al.*, Methods Mol. Biol., 269:205-18 (2004)).

30 E. *In vivo* bioluminescence imaging

Viral replication levels were quantitatively compared within the tumor administered through different routes of injection. TC-1 tumor bearing mice (tumor size = 8-10mm) were administered by either intraperitoneal (i.p.) or intra-tumoral (i.t.) injection of 1×10^7 pfu/mouse of vaccinia-luc in 200 µL phosphate-buffered saline. Bioluminescence imaging

was conducted on days 1, 3, and 7 after virus injection on a cryogenically cooled IVIS system (Xenogen/Caliper Life Sciences). The region of interest (ROI) as manually drawn over tumor areas by using Living Image software 2.5 (Xenogen/Caliper Life Sciences).

5 **F. Characterization of CD31⁺ cells infected by vaccinia**

The frequency of CD31⁺ cells infected by vaccinia virus after TC-1 tumor bearing mice (tumor size = 8-10mm) were administered by either intraperitoneal (i.p.) or intra-tumoral (i.t.) injection of 1×10^7 pfu vaccinia-GFP in 200 μ L phosphate-buffered saline were characterized. Tumor cells were harvested 24 hours after viral injection, made into single
10 cell suspensions, and subjected to CD31 staining.

In order to evaluate for killing of CD31⁺ cells, TC-1 tumors were grown in C57BL/6 mice and harvested as tumor size reached 8-10 mm. Tumors were dissociated into single cell suspensions and seeded (3×10^5 /well) into 24-well microtiter plate in complete medium. At 24 hours, Vac-WT or Vac-OVA at 0.5 MOI were added to each well, and at 48 hours,
15 the complete medium was changed and activated OT-1 T cells were added to each well at an effector-to-target ratio of 1:1 (E/T = 1:1). Cells were then harvested 4 hours later and stained with PE anti-mouse CD31 mAb and 7-AAD, and analyzed by flow cytometry using the FACSCalibur flow cytometer, and CellQuest software (Becton Dickinson, San Jose, CA). Data are presented as absolute numbers of CD31⁺7-AAD⁻ cells per 3×10^5 cells.

20

G. Heterologous prime-boost immunization

Groups of mice (five per group) were inoculated with either B16/F10 cells or TC-1 cells (5×10^4 /mouse) at Day 0. Mice were then primed with 2 μ g of either control pcDNA3, p-OVA or p-CRT/E7 DNA by gene-gun at day 5, and were boosted with i.t. injection
25 (1×10^7 pfu/mouse, in 200 μ L PBS) of Vac-WT, Vac-OVA, or Vac-CRT/E7 at day 12.

H. Evaluation of frequency of E7-specific CD8⁺ T cells by intracellular cytokine staining and flow cytometry analysis

For characterization of E7-specific CD8⁺ T cells, both splenocytes and tumor
30 xenografts were harvested 1 week after last immunization. Prior to intracellular cytokine staining, 2×10^6 pooled splenocytes and pooled tumors from each treatment group were separately incubated for 16 hours with either an H-2K^b-restricted peptide (SIINFEKL; 1.0 μ M) or an I-A^b-restricted peptide (LSQAVHAAHAEINEAGR; 1.0 μ M). In addition, 2×10^6 pooled splenocytes and pooled tumors from each treatment group were incubated for

16 hours with 1 µg/ml of E7 peptide (aa 49-57) containing an MHC class I epitope for detecting E7-specific CD8⁺ T cell precursors (Feltkamp *et al.*, Eur. J Immunol., 23:2242-9 (1993)). Cells were then harvested, stained for CD8 and IFN-γ using previously described standard protocols (Cheng *et al.*, J Clin. Invest., 108:669-78 (2001)). Samples were
5 analyzed on a FACSCalibur flow cytometer, using CellQuest software (Becton Dickinson, San Jose, CA). All of the analyses shown were carried out on a gated lymphocyte population.

I. *In vitro* cytotoxicity assay

10 Luciferase-expressing TC-1 tumor cells were added to 96-well plates at a dose of 2×10^4 /well. After 24 hours, Vac-WT or Vac-OVA (MOI = 0.5) were added to each well. At 48 hours, the complete medium was changed and activated OT-1 T cells at an E:T ratio of 1:1 were added to each well. Bioluminescence imaging was performed 4 hours later. The degree of CTL-mediated killing of the tumor cells was indicated by the decrease of
15 luminescence activity using the IVIS luminescence imaging system series 200. Bioluminescence signals were acquired for 10 seconds.

J. Statistical analysis

Statistical analysis was performed using Prism 3.0 software (GraphPad, San Diego,
20 USA). All data are expressed as means ± standard deviation (SD) and are representative of at least two independent experiments. Comparisons between individual data points were made using a Student's *t*-test or repeated measure ANOVA (analysis of variance) test, as appropriate. Tumor size was measured during the treatment twice a week by digital calipers and tumor volume (mm³) was calculated using the following equation: (tumor
25 length x width x height) / 2. Death of mouse was arbitrarily defined as tumor diameter greater than 2 cm. Differences in survival between experimental groups were analyzed using the Log rank test. A *p*-value of ≤ 0.05 was set for the significance of difference among groups.

30

Example 2: Tumor-bearing mice primed with DNA encoding a foreign antigen and treated with intratumoral injection of vaccinia virus encoding the same foreign antigen led to significant therapeutic anti-tumor effects

Intratumoral injection of vaccinia encoding a marker gene, such as luciferase, was recently demonstrated to result in significant expression of luciferase within the tumor, indicating that intratumoral injection of vaccinia can lead to significant viral infection of the tumor cells (Figure 1). Thus, in order to determine the antitumor effects generated in tumor-bearing mice primed with DNA encoding a foreign antigen, such as OVA, and treated with intratumoral injection of vaccinia virus encoding the same foreign antigen, groups of C57BL/6 mice (5 per group) were first challenged with B16 tumor cells and then primed with control pcDNA3 alone or pcDNA3 encoding ovalbumin (p-OVA). One week later, mice were treated with intratumoral injections of either wild-type vaccinia (Vac-WT) or vaccinia encoding OVA (Vac-OVA). Tumor-bearing mice treated with 1X PBS were used as negative controls. A graphical representation of the treatment regimen is depicted in Figure 2A. As shown in Figure 2B, tumor-bearing mice primed with the p-OVA followed by intratumoral Vac-OVA injection showed the best therapeutic antitumor effects compared to treatment with the other prime-boost regimens. Furthermore, tumor-bearing mice primed with the p-OVA prime followed by intratumoral Vac-OVA injection showed improved survival compared to treatment with the other therapeutic regimens ($p < 0.01$) (Figure 2C). Thus, the data indicate that the treatment with p-OVA followed by intratumoral Vac-OVA injection produced significant therapeutic anti-tumor effects and long-term survival in B16 tumor-bearing mice.

The same therapeutic approach was further tested using another tumor model, TC-1. Groups of C57BL/6 mice (5 per group) were first challenged with TC-1 tumor cells and then primed them with control pcDNA3 or p-OVA. One week later, mice were treated with either Vac-WT or Vac-OVA by intratumoral injection. Tumor-bearing mice treated with PBS were used as negative controls. A graphical representation of the treatment regimen is depicted in Figure 3A. As shown in Figure 3B, tumor-bearing mice treated with the p-OVA followed by intratumoral Vac-OVA injection showed the best therapeutic antitumor effects compared to treatment with the other prime-boost regimens. Furthermore, tumor-bearing mice treated with the p-OVA followed by intratumoral Vac-OVA injection showed improved survival compared to treatment with the other therapeutic regimens ($p < 0.01$; Figure 3C). Thus, the data indicated that the treatment with p-OVA followed by intratumoral Vac-OVA injection produced significant therapeutic anti-tumor effects and long-term survival in TC-1 tumor-bearing mice.

The therapeutic approach was further tested using an antigenic system specific to TC-1 tumor cells, specifically E7. It was found that vaccination with CRT/E7 DNA vaccine intradermally followed by intratumoral injection of vaccinia encoding CRT/E7 also generated significant therapeutic anti-tumor effects and long-term survival in TC-1 tumor-bearing mice (Figure 4). Taken together, the data demonstrate that the treatment with a foreign antigen-specific DNA vaccine followed by intratumoral injection of vaccinia encoding the same foreign antigen produced significant therapeutic anti-tumor effects and long-term survival in tumor-bearing mice in two different tumor models.

Example 3: Tumor-bearing mice primed with DNA encoding foreign antigen and treated with intratumoral injection of vaccinia encoding the same foreign antigen leads to significant number of foreign antigen-specific CD8⁺ T cells

In order to determine the antigen-specific CD8⁺ T cell immune response against OVA in tumor-bearing mice using the DNA prime and intratumoral viral boost model, groups of C57BL/6 mice (5 per group) were first challenged with B16 tumor cells and then treated with either pcDNA3 or p-OVA followed by intratumoral injection with either Vac-WT or Vac-OVA, as previously described in Figure 2. Tumor-bearing mice treated with 1X PBS were used as negative controls. Cells were harvested from the spleens and tumors of vaccinated mice 7 days after vaccinia injection and were characterized for the presence of OVA-specific CD8⁺ T cells using intracellular cytokine staining for IFN- γ followed by flow cytometry analysis. As shown in Figure 5, tumor-bearing mice that were treated with p-OVA followed by intratumoral Vac-OVA injection generated a significantly higher numbers/percentages of OVA-specific CD8⁺ T cells both in the spleens as well as tumors compared to tumor-bearing mice treated with the other regimens.

The antigen-specific immune responses elicited in another tumor model, TC-1, which uses a different antigenic system, E7, were also determined. Groups of C57BL/6 mice (5 per group) were first challenged with TC-1 tumor cells and then primed them with either pcDNA3 or p-CRT/E7 DNA vaccine intradermally. One week later, mice were treated with either Vac-WT or Vac-CRT/E7 by either intraperitoneal or intratumoral injection. Tumor-bearing mice treated with PBS were used as negative controls. It was observed that tumor-bearing mice that were treated with p-CRT/E7 DNA followed by intratumoral Vac-CRT/E7 injection generated a significantly higher number of E7-specific CD8⁺ T cells both in the spleens as well as tumors compared to tumor-bearing mice treated

with the other regimens (Figure 6). Taken together, the data indicate that treatment of tumor-bearing mice with a foreign antigen-specific DNA vaccine followed by intratumoral injection of vaccinia encoding the same foreign antigen leads to the strongest antigen-specific CD8⁺ T cell immune responses in the spleens and tumors.

5 OVA-specific CD4⁺ T cell immune responses in tumor-bearing mice treated with p-OVA followed by intratumoral Vac-OVA injection were also determined. It was found that while the OVA-specific CD4⁺ T cell immune responses in the spleens of treated mice were not significantly different from those in tumor-bearing mice treated with the other regimens, the OVA-specific CD4⁺ T cell immune responses within the tumors of treated
10 mice were significantly higher compared to those in tumor-bearing mice treated with the other regimens (Figure 7). Thus, the data indicate that treatment with p-OVA followed by intratumoral Vac-OVA injection leads to increased OVA-specific CD4⁺ T cell immune responses in the tumors, but not in the spleens of tumor-bearing mice.

In order to determine the subset of immune cells that are important for the observed
15 antitumor effects, *in vivo* antibody depletion experiments were performed in tumor-bearing mice treated with the p-OVA followed by intratumoral Vac-OVA injection. It was found that mice depleted of CD8⁺ T cells showed a significant reduction in survival compared to treated mice without depletion in both tumor models (Figure 8). Furthermore, depletion of CD4⁺ T cells showed a slight reduction in survival, although not as significant as CD8⁺ T
20 cell depletion. Taken together, the data indicate that CD8⁺ T cells, as well as CD4⁺ T cells, play an important role in the antitumor effects observed in mice treated with p-OVA followed by intratumoral Vac-OVA injection.

Example 4: Treatment with OVA expressing vaccinia not only kills the tumor cells directly, but also renders tumor cells more susceptible to killing by OVA-specific T cells

In order to determine if treatment of tumor cells with Vac-OVA renders tumor cells more susceptible to viral oncolysis as well as OVA-specific T cell-mediated killing, a cytotoxicity assay was performed using luciferase-expressing TC-1 tumor cells. TC-1/luc
30 tumor cells were plated on Day 0 and treated with either Vac-OVA or Vac-WT on Day 1. The cells were then treated with or without OVA-specific CD8⁺ T cells (OT-1 T cells) on Day 2 as shown in Figure 9A. Four hours later, the CTL-mediated killing of the TC-1 tumor cells in each well was monitored using bioluminescent imaging system. The degree

of CTL-mediated killing of the tumor cells was indicated by the decrease of luminescence activity. As shown in Figure 9B, it was observed that tumor cells incubated with Vac-WT or Vac-OVA alone demonstrated a significant reduction in luciferase activity, indicating that tumor killing was contributed by viral oncolysis. Furthermore, the lowest luciferase activity was observed in TC-1 cells treated with Vac-OVA in conjunction with OT-1 T cells, but not in cells treated with Vac-WT. The data indicates that the increased tumor lysis is contributed by OVA-specific cytotoxic T cell-mediated killing. Taken together, the data indicate that the treatment of tumor cells with Vac-OVA and OT-1 cells can lead to tumor lysis by a combination of viral oncolysis and OVA-specific cytotoxic T cell-mediated killing.

Example 5: Intratumoral injection of vaccinia leads to infection of CD31⁺ non-tumor cells by vaccinia

It was further investigated whether Vac-OVA treatment could exert cytotoxic effects on the surrounding non-tumor cells, including CD31⁺ endothelial and stromal cells. In order to determine the number of CD31⁺ non-tumor cells infected by vaccinia in tumor-bearing mice, groups of C57BL/6 mice (5 per group) were subcutaneously challenged with TC-1 tumor cells and treated with either intratumoral (i.t.) or intraperitoneal (i.p.) injection with Vac-GFP. Tumor cells were harvested 24 hours after vaccinia virus injection, stained for CD31 and characterized by flow cytometry analysis. As shown in Figure 10A, the percentage of CD31⁺ non-tumor cells infected with Vac-GFP was significantly higher in tumor-bearing mice injected intratumorally with Vac-GFP compared to mice injected intraperitoneally or mice treated with PBS. Thus, the data indicate that intratumoral injection of vaccinia leads to increased infection of CD31⁺ non-tumor cells by vaccinia compared to intraperitoneal injection.

Example 6: Treatment with vaccinia-OVA not only kills the surrounding CD31⁺ stromal cells in the tumor microenvironment directly but also renders them more susceptible to killing by OVA-specific T cells

It was further determined if treatment of explanted tumor injected with Vac-OVA would render the CD31⁺ non-tumor cells derived from the surrounding tumor stroma more susceptible to viral oncolysis and to OVA-specific CD8⁺ T cell-mediated killing. Therefore, explanted TC-1 tumor cells were plated in 96-well plates on day 0 and treated them with Vac-OVA or Vac-WT on day 1. The cells were then treated with or without

OVA-specific CD8⁺ T cells (OT-1 T cells) on day 2. Four hours later, the cells were analyzed by flow cytometry analysis for expression of CD31 and 7-AAD. As shown in Figure 10B, it was observed that CD31⁺ cells incubated with Vac-WT or Vac-OVA alone demonstrated a significant reduction in luciferase activity, indicating that killing was contributed by viral oncolysis. Furthermore, the lowest luciferase activity was observed in CD31⁺ cells treated with Vac-OVA and OT-1 T cells, but not in cells treated with Vac-WT, suggesting that the increased tumor lysis is contributed by OVA-specific cytotoxic T cell-mediated killing. Taken together, the data indicates that the treatment of CD31⁺ cells with Vac-OVA and OT-1 cells can lead to lysis by a combination of viral oncolysis and OVA-specific cytotoxic T cell-mediated killing.

EDITORIAL NOTE:

File No.: 2010246273

The last page of description is page no. 104 followed by Gene Sequence Listings pages 105-251 and followed by new amended claim pages 245-248.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of inducing or enhancing an antigen-specific immune response in a mammal having a tumor, comprising the steps of:
 - 5 (a) priming the mammal by administering to the mammal an effective amount of a nucleic acid composition encoding the antigen or a biologically active homolog thereof; and
 - (b) boosting the mammal by administering to the mammal an effective amount of an oncolytic virus comprising a nucleic acid encoding the antigen or the biologically active homolog thereof, wherein the oncolytic virus is administered intratumorally or peritumorally, thereby inducing or enhancing the antigen-specific immune response.
- 15 2. The method of claim 1, wherein the antigen is a tumor-associated antigen (TAA).
3. The method of claim 1 or 2, wherein the antigen is foreign to the mammal.
- 20 4. The method of any one of claims 1 to 3, wherein the antigen is selected from the group consisting of ovalbumin, HPV E6, and HPV E7.
- 25 5. The method of any one of claims 1 to 4, wherein the antigen comprises an ovalbumin protein comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:139.
6. The method of any one of claims 1 to 5, wherein the antigen comprises an HPV E6 protein comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of LSRHFMHQKRTAMFQDPQERPRKLPQ and AMFQDPQERPRKLPQLCTELQTTIHDIILEC.
- 30

7. The method of any one of claims 1 to 6, wherein the antigen comprises an HPV E7 protein comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of PTLHEYMLDLQPETTDLYCYEQ, HEYMLDLQPET, TLHEYMLDLQPETTD, 5 EYMLDLQPETTDLY, DEIDGPAGQAEPDRAHY and GPAGQAEPDRAHYNI.
8. The method of any one of claims 1 to 7, wherein the nucleic acid composition is a DNA vaccine.
- 10 9. The method of any one of claims 1 to 8, wherein the nucleic acid composition is administered from the group consisting of intradermally, intraperitoneally, and intravenously.
- 15 10. The method of any one of claims 1 to 9, wherein the mammal is a human having a tumor and wherein the nucleic acid composition is administered intratumorally or peritumorally.
- 20 11. The method of any one of claims 1 to 10, wherein the oncolytic virus is selected from the group consisting of vaccinia virus, adenovirus, herpes simplex virus, poxvirus, vesicular stomatitis virus, measles virus, Newcastle disease virus, influenza virus, and reovirus.
- 25 12. The method of any one of claims 1 to 11, wherein the oncolytic virus is thymidine kinase negative.
13. The method of any one of claims 1 to 12, wherein the nucleic acid composition is present within an oncolytic virus.
- 30 14. The method of claim 13, wherein the oncolytic virus of step (a) is the same as or is different from the oncolytic virus of step (b).

15. The method of any one of claims 1 to 14, wherein step (a) is performed before step (b), step (a) and step (b) are performed at the same time, or step (a) is performed after step (b).
- 5 16. The method of any one of claims 1 to 15, wherein step (a) and/or step (b) is repeated at least once.
17. The method of any one of claims 1 to 16, wherein the dosage used in step (a) and/or step (b) is 1×10^7 pfu.
- 10 18. The method of any one of claims 1 to 17, wherein the antigen-specific immune response is greater in magnitude than an antigen-specific immune response induced by administration of the nucleic acid composition alone.
- 15 19. The method of any one of claims 1 to 18, wherein the antigen-specific immune response is mediated at least in part by $CD8^+$ cytotoxic T lymphocytes (CTL).
20. The method of any one of claims 1 to 19, wherein the antigen-specific immune response is mediated at least in part by $CD8^+$ cytotoxic T lymphocytes (CTL).
- 20 21. The method of any one of claims 1 to 20, wherein the antigen-specific immune response is mediated at least in part by peritumoral stromal cells.
22. The method of any one of claims 1 to 21, further comprising administering an
- 25 effective amount of a chemotherapeutic agent.
23. The method of any one of claims 1 to 22, further comprising screening the mammal for the presence of antibodies against the antigen.
- 30 24. The method of any one of claims 1 to 23, wherein the mammal is a human.

25. The method of any one of claims 1 to 24, wherein the tumor is of an advanced stage cancer.

5 26. The method of claim 25, wherein the advanced stage cancer tumor is melanoma or thymoma.

27. A kit when used in any one of the methods of claims 1 to 26 comprising a priming composition and a boosting composition, the kit comprising;

10 (a) a priming composition comprising DNA encoding an immunogenic foreign antigen and a pharmaceutically acceptable carrier; and

(a) a boosting composition comprising a virus encoding said foreign antigen and a pharmaceutically acceptable carrier.

15

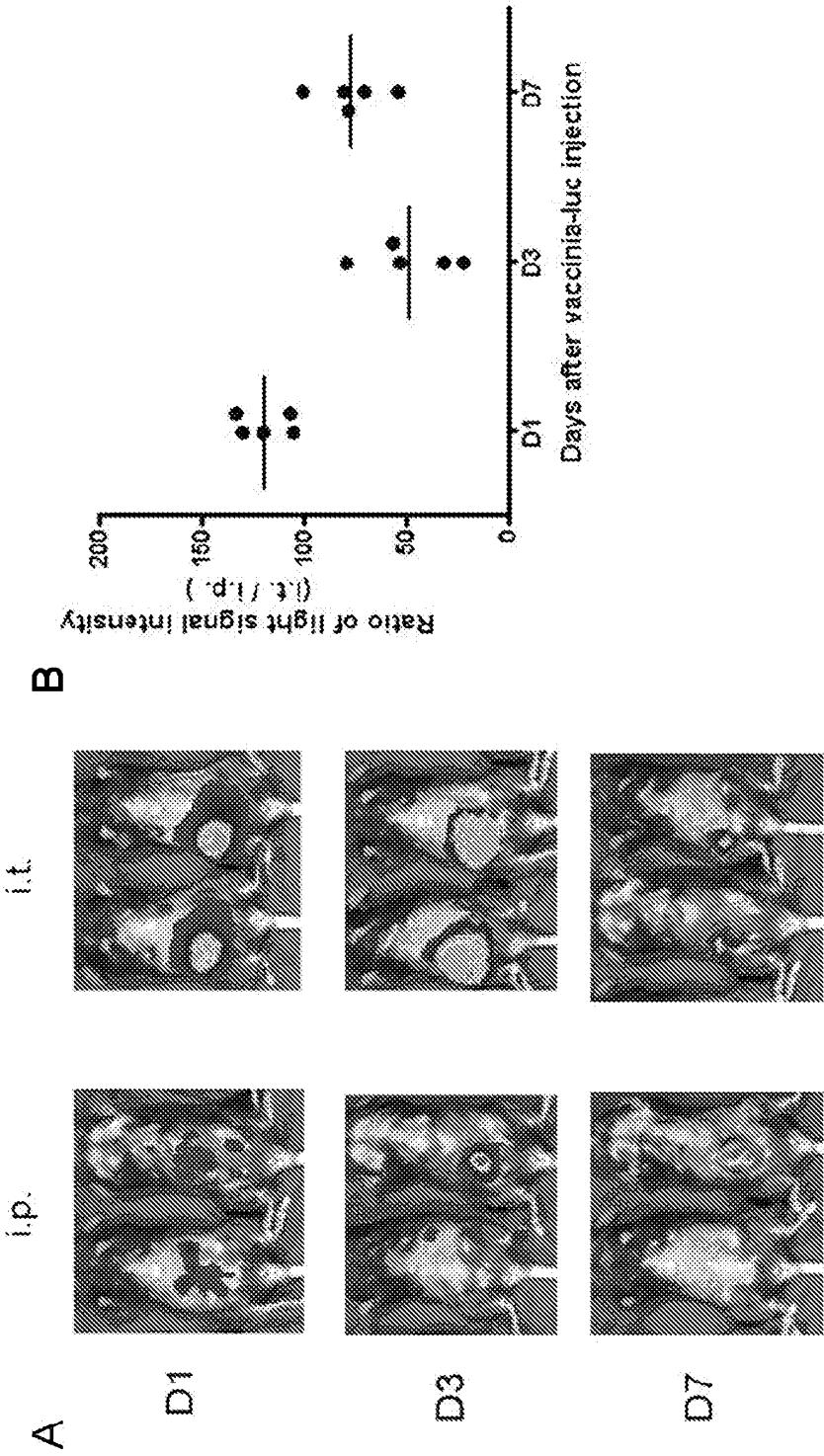


Figure 1

Figure 2

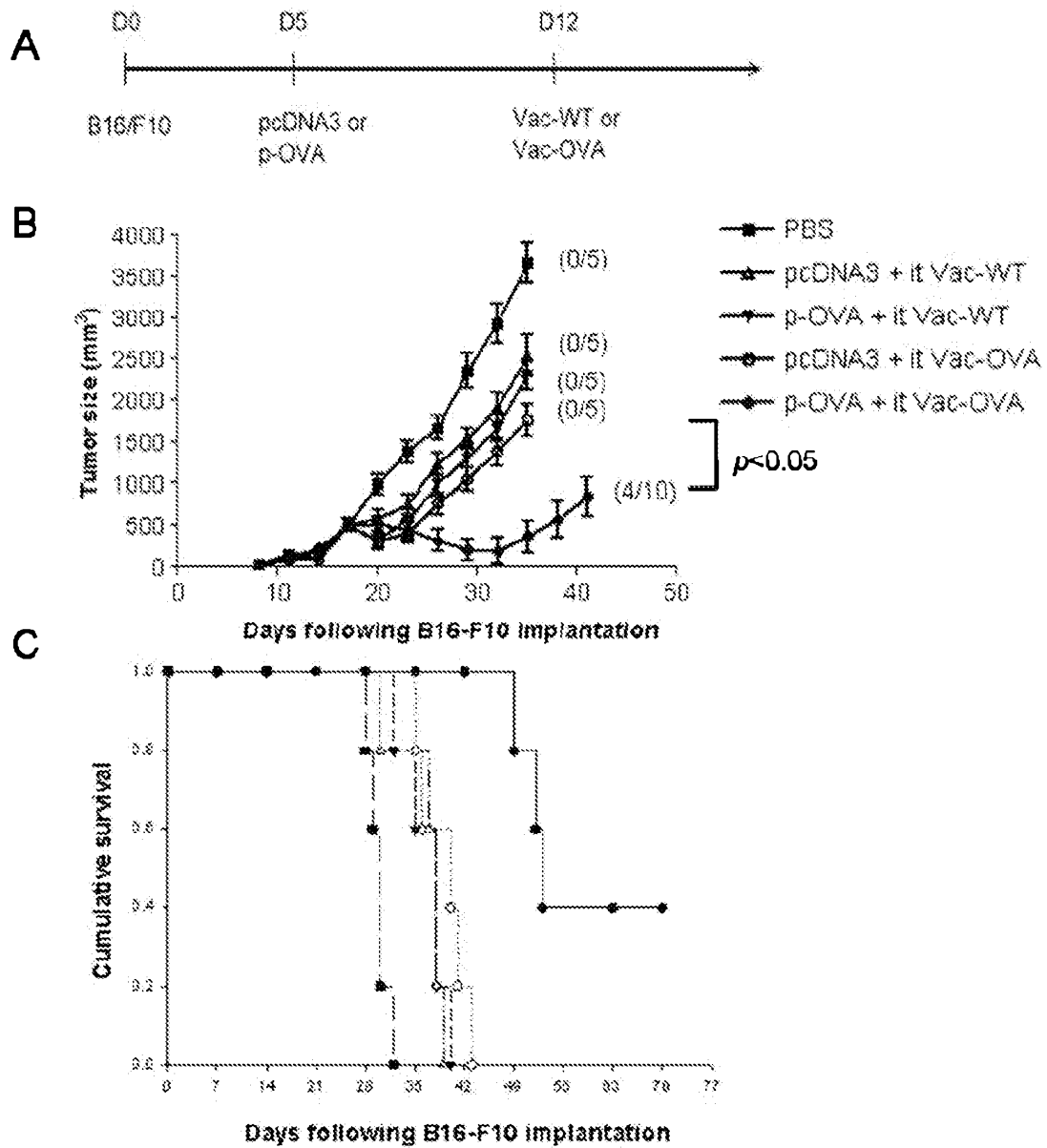


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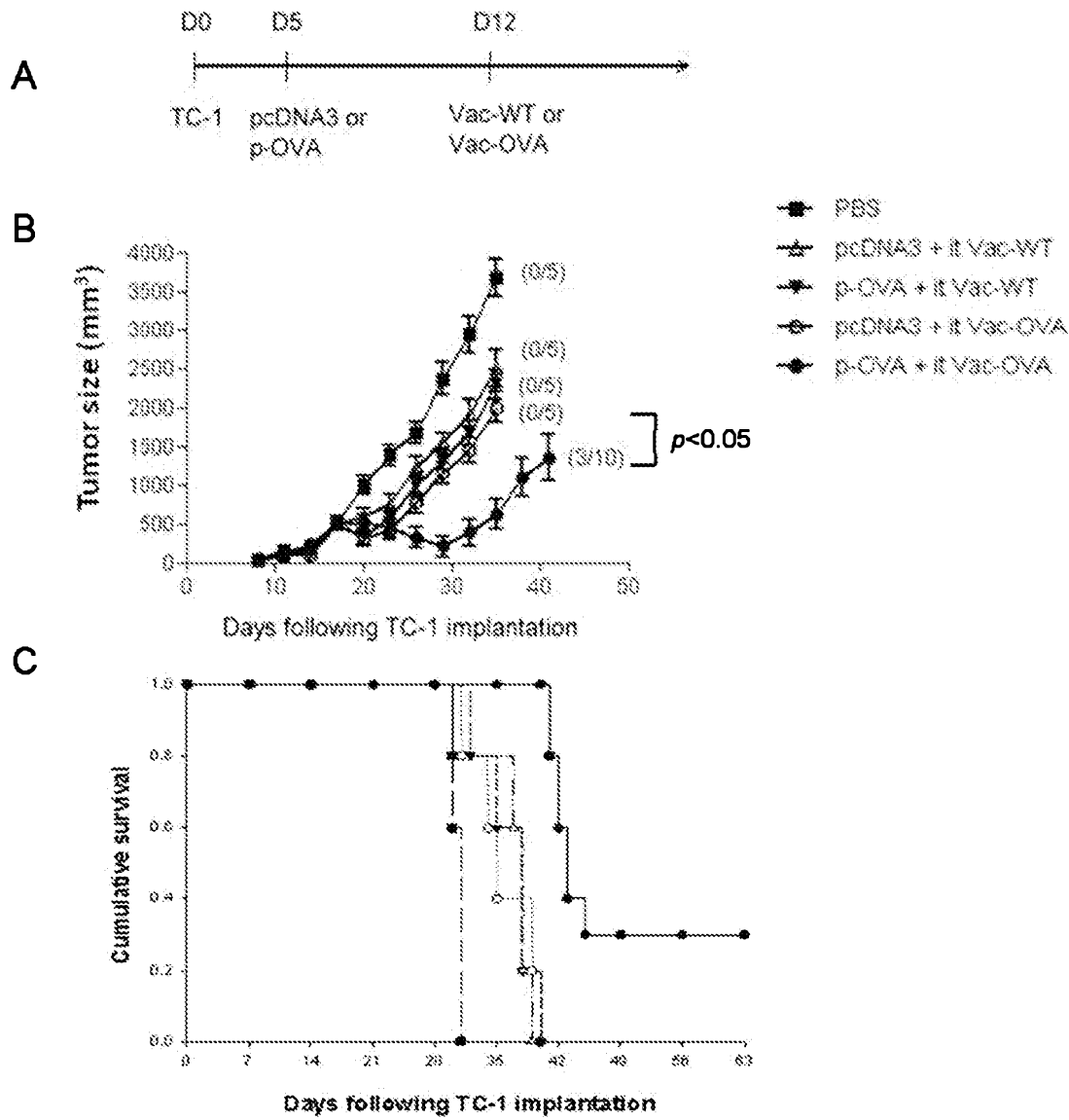


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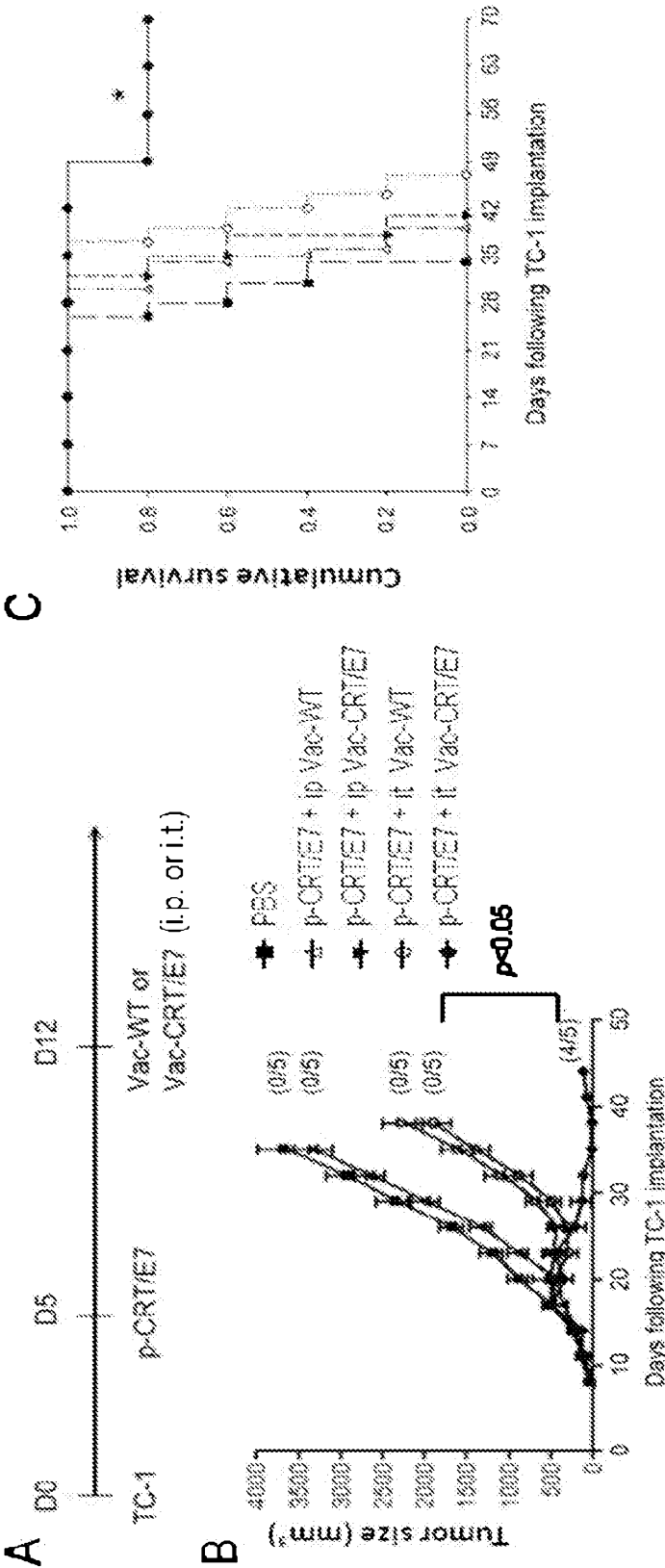
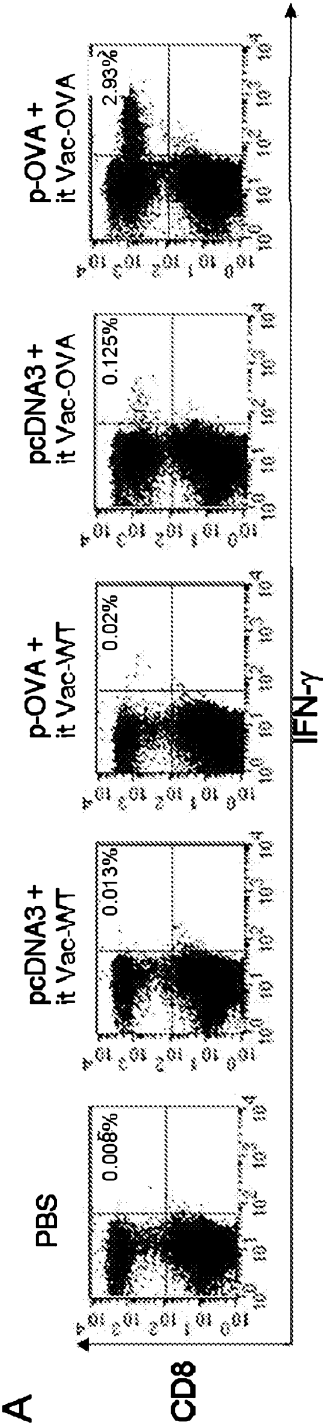


Figure 5



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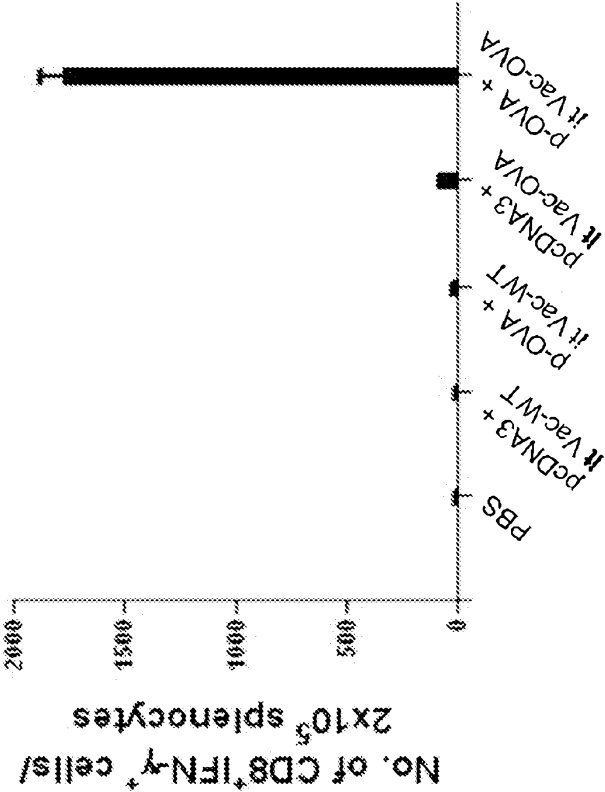
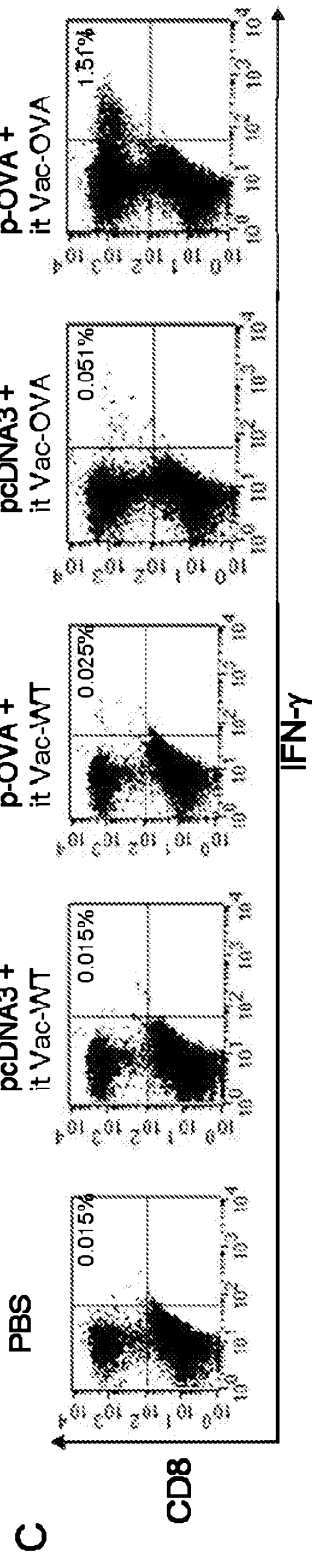


Figure 5 (cont.)



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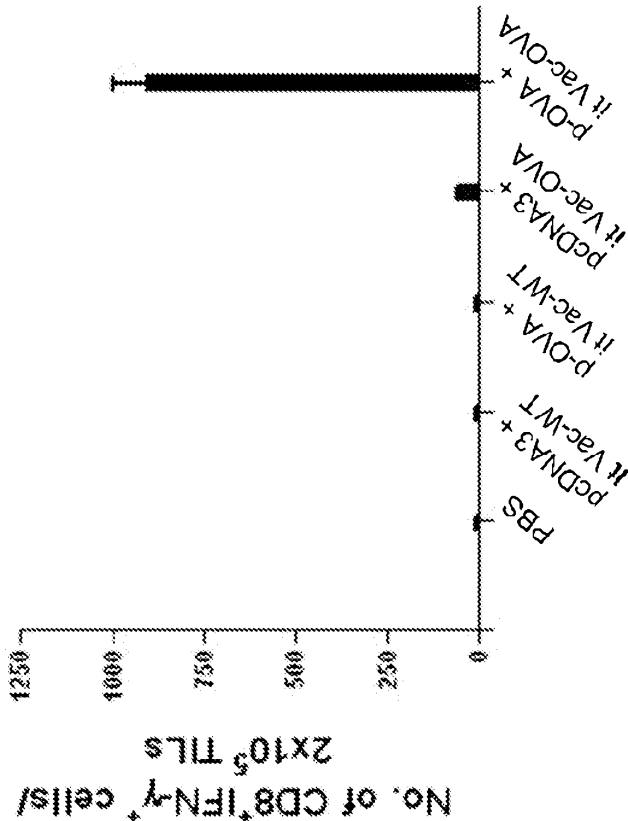


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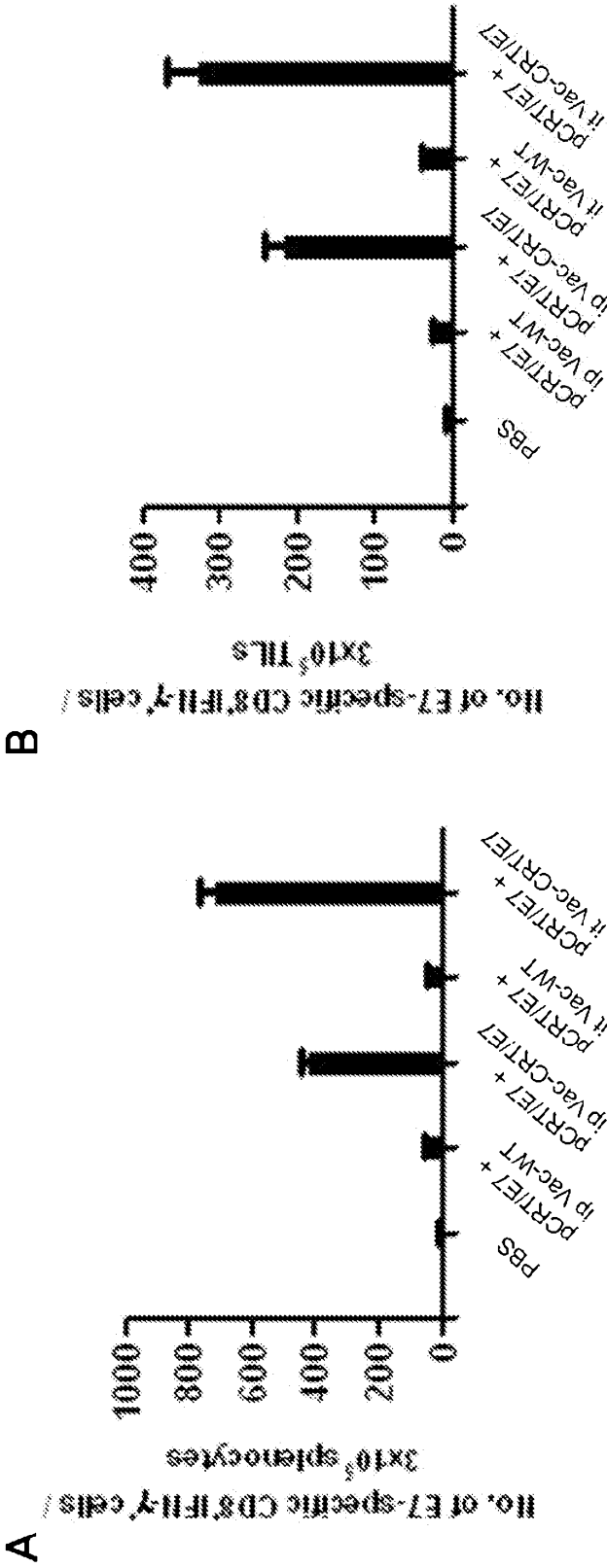


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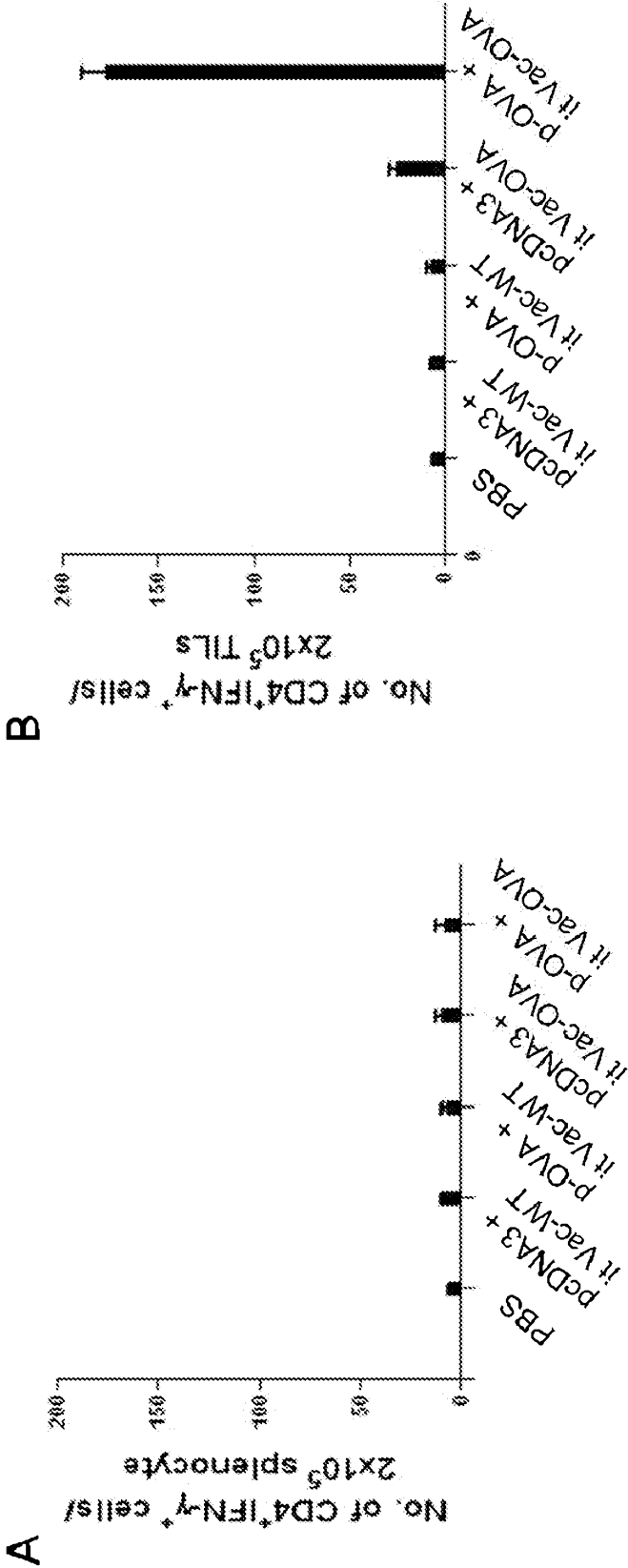


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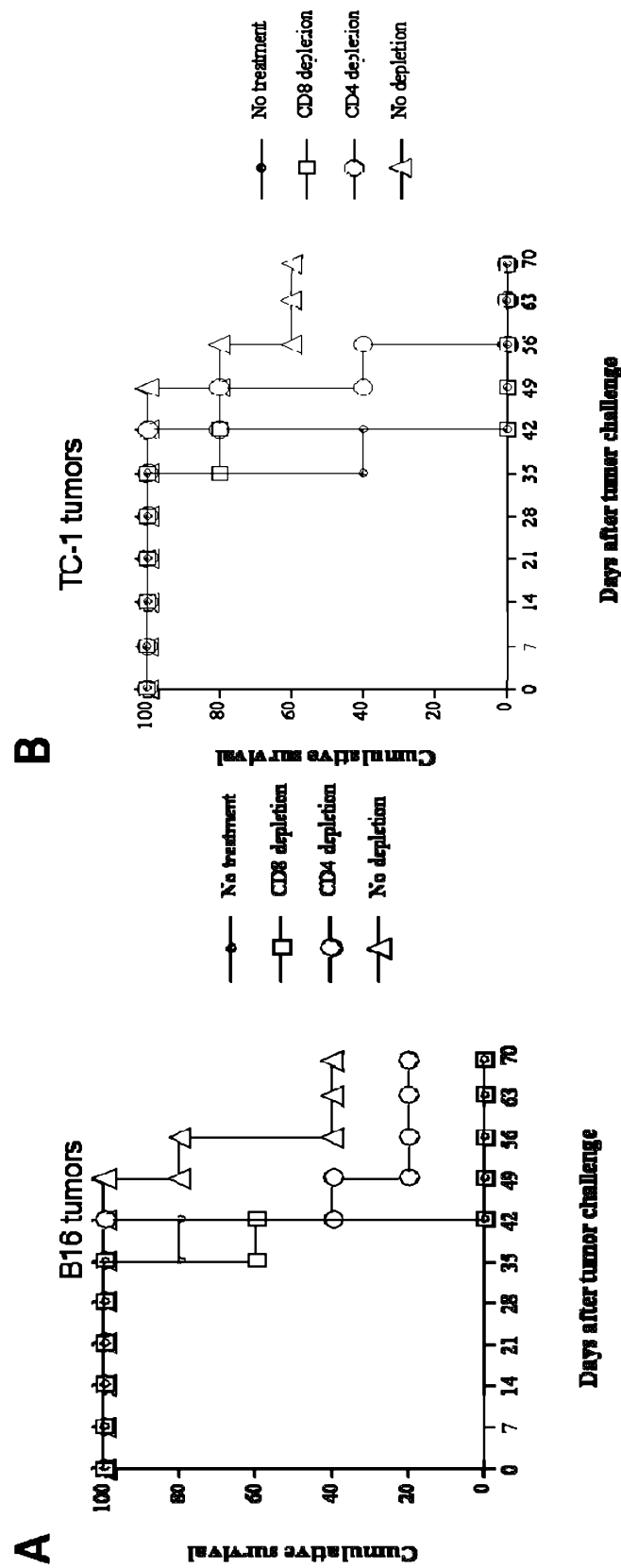


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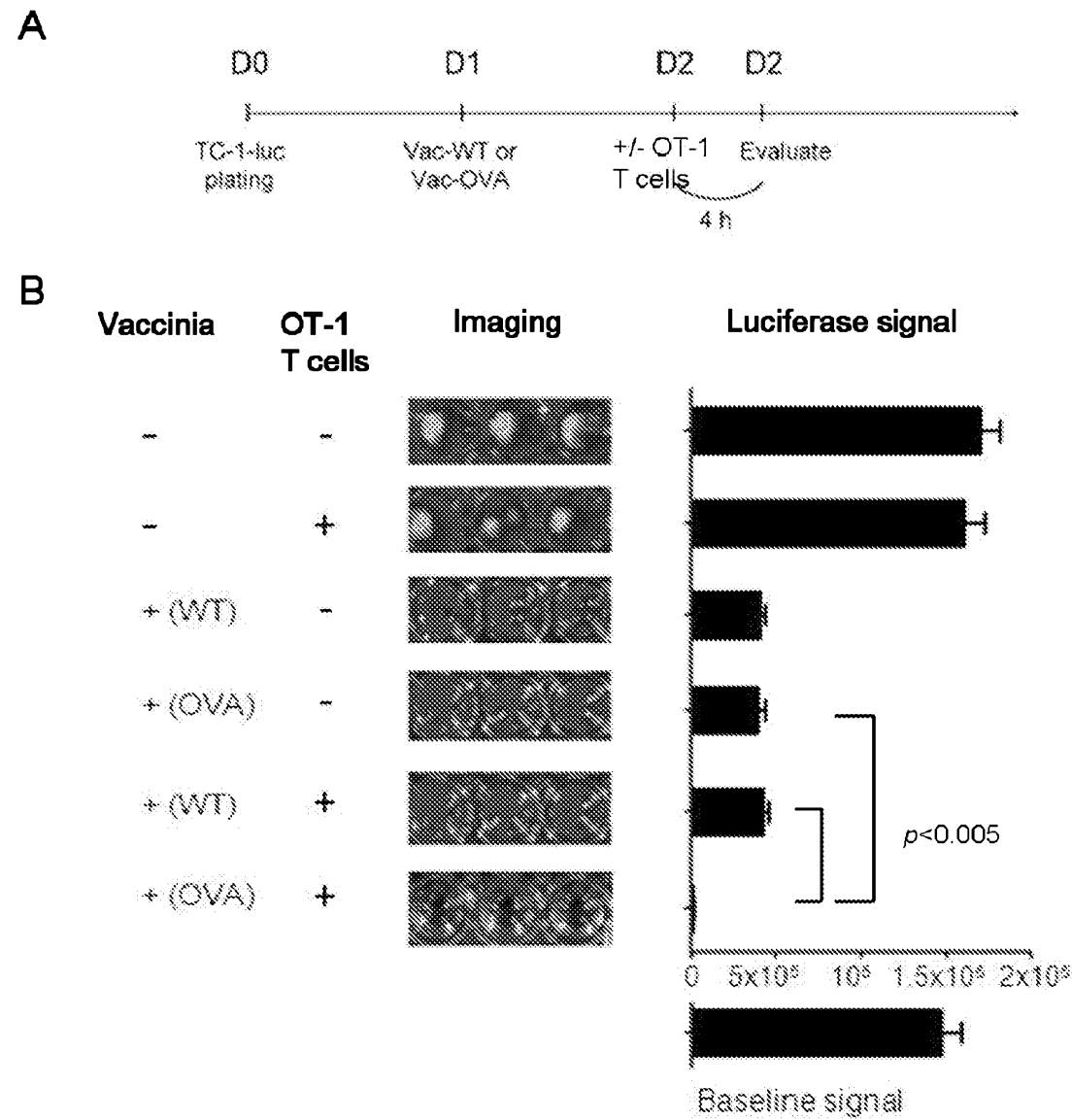
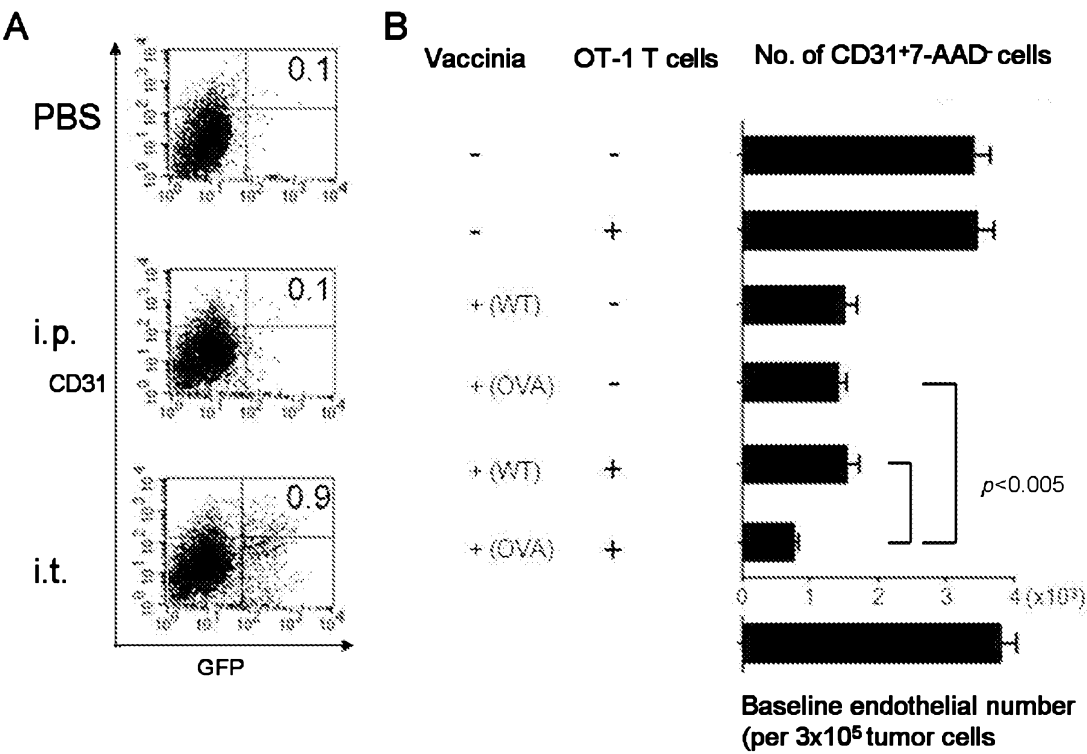


Figure 10



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	atctacgaag cagctcaggc tgcgtcacag gccactggcg ctgccacccc cggcggcgag	1800
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	Met Lys Leu Lys Arg Asp Ala Glu Ala Tyr Leu Gly Glu Asp Ile Thr 100 105 110	

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	Asp	Ala	Val	Ile	Thr	Thr	Pro	Ala	Tyr	Phe	Asn	Asp	Ala	Gln	Arg	Gln	
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5	Ala	Thr	Lys	Asp	Ala	Gly	Gln	Ile	Ala	Gln	Val	Leu	Arg	Ile	Val	Asn	
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25	Asn	His	Leu	Gly	Gly	Asp	Asp	Trp	Asp	Gln	Arg	Val	Val	Asp	Trp	Leu	
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	Pro	Glu	Thr	Thr	Asp	Leu	Tyr	Cys	Tyr	Glu	Gln	Leu	Asn	Asp	Ser	Ser	
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5		aga gcc cat tac aat att gta acc ttt tgt tgc aag tgt gac tct acg	192
		Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp Ser Thr	
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		Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln	
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		Gly Ser Met Ala Arg Ala Val Gly Ile Asp Leu Gly Thr Thr Asn Ser	
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		Glu Gly Ser Arg Thr Thr Pro Ser Ile Val Ala Phe Ala Arg Asn Gly	
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		Arg Ala Thr Ser Gly Asp Asn His Leu Gly Gly Asp Asp Trp Asp Gln	
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85		cgg gtc gtc gat tgg ctg gtg gac aag ttc aag ggc acc agc ggc atc	960
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		Asp Leu Thr Lys Asp Lys Met Ala Met Gln Arg Leu Arg Glu Ala Ala	
		325 330 335	

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		gag aag gca aag atc gag ctg agt tcg agt cag tcc acc tcg atc aac	1056
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		atg ccc gcg gtg acc gat ctg gtc aag gaa ctc acc ggc ggc aag gaa	1296
		Met Pro Ala Val Thr Asp Leu Val Lys Glu Leu Thr Gly Gly Lys Glu	
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		Asp Val Thr Pro Leu Ser Leu Gly Ile Glu Thr Lys Gly Gly Val Met	
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75		cag cgt gag gcc gag ggt ggt tcg aag gta cct gaa gac acg ctg aac	1920
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10	cag gct ctg ggg caa gcg atc tac gaa gca gct cag gct gcg tca cag Gln Ala Leu Gly Gln Ala Ile Tyr Glu Ala Ala Gln Ala Ala Ser Gln 675 680 685	2064
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	Gly Ser Met Ala Arg Ala Val Gly Ile Asp Leu Gly Thr Thr Asn Ser 100 105 110	
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	Ile Glu Ile Asp Gly Lys Lys Tyr Thr Ala Pro Glu Ile Ser Ala Arg 180 185 190	
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	cagccatgcc ggggtcagcg tggatcatgg ccagaccag ccgcgccggg aaaagcgctg	1380
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65	ggaaggcggg cgcttgaga ccattctcgg ctggccgctg gccgagcgca ccgtggtgat	2520
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<212> PRT

<213> *Pseudomonas aeruginosa*

<400> 24

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15 Trp Asn Glu Cys Ala Lys Ala Cys Val Leu Asp Leu Lys Asp Gly Val
35 40 45

20 Arg Ser Ser Arg Met Ser Val Asp Pro Ala Ile Ala Asp Thr Asn Gly
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25 Gln Gly Val Leu His Tyr Ser Met Val Leu Glu Gly Gly Asn Asp Ala
65 70 75 80

30 Leu Lys Leu Ala Ile Asp Asn Ala Leu Ser Ile Thr Ser Asp Gly Leu
85 90 95

35 Thr Ile Arg Leu Glu Gly Gly Val Glu Pro Asn Lys Pro Val Arg Tyr
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40 Ser Tyr Thr Arg Gln Arg Ser Trp Ser Leu Asn Trp Leu Val Pro Ile
115 120 125

45 Gly His Glu Lys Pro Ser Asn Ile Lys Val Phe Ile His Glu Leu Asn
130 135 140

50 Ala Gly Asn Gln Leu Ser His Met Ser Pro Ile Tyr Thr Ile Glu Met
145 150 155 160

55 Gly Asp Glu Leu Leu Ala Lys Leu Ala Arg Asp Ala Thr Phe Phe Val
165 170 175

60 Arg Ala His Glu Ser Asn Glu Met Gln Pro Thr Leu Ala Ile Ser His
180 185 190

65 Ala Gly Val Ser Val Val Met Ala Gln Thr Gln Pro Arg Arg Glu Lys
195 200 205

70 Arg Trp Ser Glu Trp Ala Ser Gly Lys Val Leu Cys Leu Leu Asp Pro
210 215 220

75 Leu Asp Gly Val Tyr Asn Tyr Leu Ala Gln Gln Arg Cys Asn Leu Asp
225 230 235 240

Asp Thr Trp Glu Gly Lys Ile Tyr Arg Val Leu Ala Gly Asn Pro Ala
245 250 255

Lys His Asp Leu Asp Ile Lys Pro Thr Val Ile Ser His Arg Leu His
260 265 270

Phe Pro Glu Gly Gly Ser Leu Ala Ala Leu Thr Ala His Gln Ala Cys
275 280 285

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10	Tyr	Leu	Ala	Ala	Arg	Leu	Ser	Trp	Asn	Gln	Val	Asp	Gln	Val	Ile	Arg
					325					330					335	
15	Asn	Ala	Leu	Asp	Gly	Ser	Gly	Gly	Asp	Leu	Gly	Glu	Ala	Ile	Arg	Glu
				340					345					350		
20	Gln	Pro	Glu	Gln	Ala	Arg	Leu	Ala	Leu	Thr	Leu	Ala	Ala	Ala	Glu	Ser
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25	Phe	Val	Arg	Gln	Gly	Thr	Gly	Asn	Asp	Glu	Ala	Gly	Ala	Ala	Asn	Ala
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35	Pro	Ala	Asp	Ser	Gly	Asp	Ala	Leu	Leu	Glu	Arg	Asn	Tyr	Pro	Thr	Gly
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40	Ala	Glu	Phe	Leu	Gly	Asp	Gly	Gly	Asp	Val	Ser	Phe	Ser	Thr	Arg	Gly
				420					425					430		
45	Thr	Gln	Asn	Trp	Thr	Val	Glu	Arg	Leu	Leu	Gln	Ala	His	Arg	Gln	Leu
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50	Glu	Glu	Arg	Gly	Tyr	Val	Phe	Val	Gly	Tyr	His	Gly	Thr	Phe	Leu	Glu
	450						455					460				
55	Ala	Ala	Gln	Ser	Ile	Val	Phe	Gly	Gly	Val	Arg	Ala	Arg	Ser	Gln	Asp
	465					470					475					480
60	Leu	Asp	Ala	Ile	Trp	Arg	Gly	Phe	Tyr	Ile	Ala	Gly	Asp	Pro	Ala	Tyr
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65	Gly	Tyr	Ala	Gln	Asp	Gln	Glu	Pro	Asp	Arg	Arg	Ile	Arg	Asn	Gly	Ala
				500					505					510		
70	Leu	Leu	Arg	Val	Tyr	Val	Pro	Arg	Ser	Ser	Leu	Pro	Gly	Phe	Tyr	Arg
			515					520					525			
75	Thr	Ser	Leu	Thr	Leu	Ala	Ala	Pro	Glu	Ala	Ala	Gly	Glu	Val	Glu	Arg
	530					535						540				
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	545					550					555					560
85	Glu	Glu	Glu	Gly	Gly	Arg	Leu	Glu	Thr	Ile	Leu	Gly	Trp	Pro	Leu	Ala
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90	Glu	Arg	Thr	Val	Val	Ile	Pro	Ser	Ala	Ile	Pro	Thr	Asp	Pro	Arg	Asn
				580					585					590		

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Val Gly Gly Asp Leu Asp Pro Ser Ser Ile Pro Asp Lys Glu Gln Ala
595 600 605

5 Ile Ser Ala Leu Pro Asp Tyr Ala Ser Gln Pro Gly Lys Pro Pro Arg
610 615 620

10 Glu Asp Leu Lys
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<211> 167
<212> PRT
<213> Pseudomonas aeruginosa

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20 25 30

30 Arg Gly Trp Glu Gln Leu Glu Gln Cys Gly Tyr Pro Val Gln Arg Leu
35 40 45

35 Val Ala Leu Tyr Leu Ala Ala Arg Leu Ser Trp Asn Gln Val Asp Gln
50 55 60

40 Val Ile Arg Asn Ala Leu Asp Gly Ser Gly Gly Asp Leu Gly Glu Ala
65 70 75 80

45 Ile Arg Glu Gln Pro Glu Gln Ala Arg Leu Ala Leu Thr Leu Ala Ala
85 90 95

50 Ala Glu Ser Phe Val Arg Gln Gly Thr Gly Asn Asp Glu Ala Gly Ala
100 105 110

55 Ala Asn Ala Asp Val Val Ser Leu Thr Cys Pro Val Ala Ala Gly Glu
115 120 125

60 Cys Ala Gly Pro Ala Asp Ser Gly Asp Ala Leu Leu Glu Arg Asn Tyr
130 135 140

65 Pro Thr Gly Ala Glu Phe Leu Gly Asp Gly Gly Asp Val Ser Phe Ser
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70 Thr Arg Gly Thr Gln Asn Trp
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75 <210> 26
<211> 870
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<220>
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<222> (1) .. (867)

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	1			5						10					15		
15	cac	cag	gct	tgc	cac	ctg	ccg	ctg	gag	act	ttc	acc	cgt	cat	cgc	cag	144
	His	Gln	Ala	Cys	His	Leu	Pro	Leu	Glu	Thr	Phe	Thr	Arg	His	Arg	Gln	
20				20					25					30			192
	ccg	cgc	ggc	tgg	gaa	caa	ctg	gag	cag	tgc	ggc	tat	ccg	gtg	cag	cgg	
25	Pro	Arg	Gly	Trp	Glu	Gln	Leu	Glu	Gln	Cys	Gly	Tyr	Pro	Val	Gln	Arg	240
		35					40						45				
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	Leu	Val	Ala	Leu	Tyr	Leu	Ala	Ala	Arg	Leu	Ser	Trp	Asn	Gln	Val	Asp	
35		50				55					60						336
	cag	gtg	atc	cgc	aac	gcc	ctg	gcc	agc	ccc	ggc	agc	ggc	ggc	gac	ctg	
40	Gln	Val	Ile	Arg	Asn	Ala	Leu	Ala	Ser	Pro	Gly	Ser	Gly	Gly	Asp	Leu	384
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	Gly	Glu	Ala	Ile	Arg	Glu	Gln	Pro	Glu	Gln	Ala	Arg	Leu	Ala	Leu	Thr	
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	Asp	Glu	Ala	Gly	Ala	Ala	Asn	Ala	Asp	Val	Val	Ser	Leu	Thr	Cys	Pro	
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	gtc	gcc	gcc	ggt	gaa	tgc	gcg	ggc	ccg	gcg	gac	agc	ggc	gac	gcc	ctg	
70	Val	Ala	Ala	Gly	Glu	Cys	Ala	Gly	Pro	Ala	Asp	Ser	Gly	Asp	Ala	Leu	672
		130				135					140						
75	ctg	gag	cgc	aac	tat	ccc	act	ggc	gcg	gag	ttc	ctc	ggc	gac	ggc	ggc	720
	Leu	Glu	Arg	Asn	Tyr	Pro	Thr	Gly	Ala	Glu	Phe	Leu	Gly	Asp	Gly	Gly	
80		145			150					155						160	768
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85	Asp	Val	Ser	Phe	Ser	Thr	Arg	Gly	Thr	Gln	Asn	Glu	Phe	Met	His	Gly	816
				165					170					175			
90	gat	aca	cct	aca	ttg	cat	gaa	tat	atg	tta	gat	ttg	caa	cca	gag	aca	864
	Asp	Thr	Pro	Thr	Leu	His	Glu	Tyr	Met	Leu	Asp	Leu	Gln	Pro	Glu	Thr	
95			180					185					190				870
	act	gat	ctc	tac	tgt	tat	gag	caa	tta	aat	gac	agc	tca	gag	gag	gag	
100	Thr	Asp	Leu	Tyr	Cys	Tyr	Glu	Gln	Leu	Asn	Asp	Ser	Ser	Glu	Glu	Glu	96
			195			200						205					
105	gat	gaa	ata	gat	ggt	cca	gct	gga	caa	gca	gaa	ccg	gac	aga	gcc	cat	144
	Asp	Glu	Ile	Asp	Gly	Pro	Ala	Gly	Gln	Ala	Glu	Pro	Asp	Arg	Ala	His	
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	tac	aat	att	gta	acc	ttt	tgt	tgc	aag	tgt	gac	tct	acg	ctt	cgg	ttg	
115	Tyr	Asn	Ile	Val	Thr	Phe	Cys	Cys	Lys	Cys	Asp	Ser	Thr	Leu	Arg	Leu	240
		225				230					235					240	
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	Cys	Val	Gln	Ser	Thr	His	Val	Asp	Ile	Arg	Thr	Leu	Glu	Asp	Leu	Leu	
125				245					250					255			336
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130	Met	Gly	Thr	Leu	Gly	Ile	Val	Cys	Pro	Ile	Cys	Ser	Gln	Gly	Ser	Glu	384
			260					265					270				
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	Leu	Gly	Thr	Lys	Leu	Lys	Phe	Lys	Pro	Leu	Ile	Ser	Leu	Asp	Cys	Ala	
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145	Phe																528

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<212> PRT
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

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His Gln Ala Cys His Leu Pro Leu Glu Thr Phe Thr Arg His Arg Gln
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25

Pro Arg Gly Trp Glu Gln Leu Glu Gln Cys Gly Tyr Pro Val Gln Arg
35 40 45

30

Leu Val Ala Leu Tyr Leu Ala Ala Arg Leu Ser Trp Asn Gln Val Asp
50 55 60

35

Gln Val Ile Arg Asn Ala Leu Ala Ser Pro Gly Ser Gly Gly Asp Leu
65 70 75 80

40

Gly Glu Ala Ile Arg Glu Gln Pro Glu Gln Ala Arg Leu Ala Leu Thr
85 90 95

45

Leu Ala Ala Ala Glu Ser Glu Arg Phe Val Arg Gln Gly Thr Gly Asn
100 105 110

50

Asp Glu Ala Gly Ala Ala Asn Ala Asp Val Val Ser Leu Thr Cys Pro
115 120 125

55

Val Ala Ala Gly Glu Cys Ala Gly Pro Ala Asp Ser Gly Asp Ala Leu
130 135 140

60

Leu Glu Arg Asn Tyr Pro Thr Gly Ala Glu Phe Leu Gly Asp Gly Gly
145 150 155 160

65

Asp Val Ser Phe Ser Thr Arg Gly Thr Gln Asn Glu Phe Met His Gly
165 170 175

70

Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr
180 185 190

75

Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser Glu Glu Glu
195 200 205

Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp Arg Ala His
210 215 220

Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp Ser Thr Leu Arg Leu
225 230 235 240

Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu Asp Leu Leu
245 250 255

Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln Gly Ser Glu

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35	atccgttgca aggatgatga gtttacacac ctgtacacac tgattgtgcg gccagacaac	540	
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50	cccgatccca gtatctatgc ctatgataac tttggcgtgc tgggcctgga cctctggcag	960	
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	Trp Thr Ser Arg Trp Ile Glu Ser Lys His Lys Ser Asp Phe Gly Lys		
	35 40 45		

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5	Phe	Val	Leu	Ser	Ser	Gly	Lys	Phe	Tyr	Gly	Asp	Glu	Glu	Lys	Asp	Lys	
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20	Val	Lys	His	Glu	Gln	Asn	Ile	Asp	Cys	Gly	Gly	Gly	Tyr	Val	Lys	Leu	
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25	Phe	Pro	Asn	Ser	Leu	Asp	Gln	Thr	Asp	Met	His	Gly	Asp	Ser	Glu	Tyr	
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35	His	Val	Ile	Phe	Asn	Tyr	Lys	Gly	Lys	Asn	Val	Leu	Ile	Asn	Lys	Asp	
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40	Ile	Arg	Cys	Lys	Asp	Asp	Glu	Phe	Thr	His	Leu	Tyr	Thr	Leu	Ile	Val	
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45	Arg	Pro	Asp	Asn	Thr	Tyr	Glu	Val	Lys	Ile	Asp	Asn	Ser	Gln	Val	Glu	
				180					185					190			
50	Ser	Gly	Ser	Leu	Glu	Asp	Asp	Trp	Asp	Phe	Leu	Pro	Pro	Lys	Lys	Ile	
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55	Lys	Asp	Pro	Asp	Ala	Ser	Lys	Pro	Glu	Asp	Trp	Asp	Glu	Arg	Ala	Lys	
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60	Ile	Asp	Asp	Pro	Thr	Asp	Ser	Lys	Pro	Glu	Asp	Trp	Asp	Lys	Pro	Glu	
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65	His	Ile	Pro	Asp	Pro	Asp	Ala	Lys	Lys	Pro	Glu	Asp	Trp	Asp	Glu	Glu	
				245						250					255		
70	Met	Asp	Gly	Glu	Trp	Glu	Pro	Pro	Val	Ile	Gln	Asn	Pro	Glu	Tyr	Lys	
			260						265					270			
75	Gly	Glu	Trp	Lys	Pro	Arg	Gln	Ile	Asp	Asn	Pro	Asp	Tyr	Lys	Gly	Thr	
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80	Trp	Ile	His	Pro	Glu	Ile	Asp	Asn	Pro	Glu	Tyr	Ser	Pro	Asp	Pro	Ser	
	290						295					300					
85	Ile	Tyr	Ala	Tyr	Asp	Asn	Phe	Gly	Val	Leu	Gly	Leu	Asp	Leu	Trp	Gln	
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90	Val	Lys	Ser	Gly	Thr	Ile	Phe	Asp	Asn	Phe	Leu	Ile	Thr	Asn	Asp	Glu	
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95	Ala	Tyr	Ala	Glu	Glu	Phe	Gly	Asn	Glu	Thr	Trp	Gly	Val	Thr	Lys	Ala	
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Ala Glu Lys Gln Met Lys Asp Lys Gln Asp Glu Glu Gln Arg Leu Lys
355 360 365

5

Glu Glu Glu Glu Asp Lys Lys Arg Lys Glu Glu Glu Glu Ala Glu Asp
370 375 380

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Lys Glu Asp Asp Glu Asp Lys Asp Glu Asp Glu Glu Asp Glu Glu Asp
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Lys Glu Glu Asp Glu Glu Glu Asp Val Pro Gly Gln Ala Lys Asp Glu
405 410 415

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Leu

<210> 30
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25 <213> Homo sapiens

<400> 30
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Attorney Docket No. JHV-087.25

<223> Description of Artificial Sequence: Synthetic polypeptide

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50	Gly Leu Ser Lys Asp Ile Phe Lys His Ile Gly Pro Asp Glu Val Ile	
	115 120 125	
55	Gly Glu Ser Met Glu Met Pro Ala Glu Val Gly Gln Lys Ser Gln Lys	
	130 135 140	
60	Arg Pro Phe Pro Glu Glu Leu Pro Ala Asp Leu Lys His Trp Lys Pro	
	145 150 155 160	
	Ala Glu Pro Pro Thr Val Val Thr Gly Ser Leu Leu Val Gly Pro Val	
	165 170 175	
65	Ser Asp Cys Ser Thr Leu Pro Cys Leu Pro Leu Pro Ala Leu Phe Asn	
	180 185 190	
70	Gln Glu Pro Ala Ser Gly Gln Met Arg Leu Glu Lys Thr Asp Gln Ile	
	195 200 205	
75	Pro Met Pro Phe Ser Ser Ser Ser Leu Ser Cys Leu Asn Leu Pro Glu	
	210 215 220	

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	Gly	Pro	Ile	Gln	Phe	Val	Pro	Thr	Ile	Ser	Thr	Leu	Pro	His	Gly	Leu	
	225					230					235					240	
5	Trp	Gln	Ile	Ser	Glu	Ala	Gly	Thr	Gly	Val	Ser	Ser	Ile	Phe	Ile	Tyr	
					245					250					255		
10	His	Gly	Glu	Val	Pro	Gln	Ala	Ser	Gln	Val	Pro	Pro	Pro	Ser	Gly	Phe	
				260					265					270			
15	Thr	Val	His	Gly	Leu	Pro	Thr	Ser	Pro	Asp	Arg	Pro	Gly	Ser	Thr	Ser	
			275					280					285				
20	Pro	Phe	Ala	Pro	Ser	Ala	Thr	Asp	Leu	Pro	Ser	Met	Pro	Glu	Pro	Ala	
		290					295					300					
25	Leu	Thr	Ser	Arg	Ala	Asn	Met	Thr	Glu	His	Lys	Thr	Ser	Pro	Thr	Gln	
	305					310					315					320	
30	Cys	Pro	Ala	Ala	Gly	Glu	Val	Ser	Asn	Lys	Leu	Pro	Lys	Trp	Pro	Glu	
					325					330					335		
35	Pro	Val	Glu	Gln	Phe	Tyr	Arg	Ser	Leu	Gln	Asp	Thr	Tyr	Gly	Ala	Glu	
				340					345					350			
40	Pro	Ala	Gly	Pro	Asp	Gly	Ile	Leu	Val	Glu	Val	Asp	Leu	Val	Gln	Ala	
			355					360					365				
45	Arg	Leu	Glu	Arg	Ser	Ser	Ser	Lys	Ser	Leu	Glu	Arg	Glu	Leu	Ala	Thr	
		370					375					380					
50	Pro	Asp	Trp	Ala	Glu	Arg	Gln	Leu	Ala	Gln	Gly	Gly	Leu	Ala	Glu	Val	
		385				390					395					400	
55	Leu	Leu	Ala	Ala	Lys	Glu	His	Arg	Arg	Pro	Arg	Glu	Thr	Arg	Val	Ile	
					405					410					415		
60	Ala	Val	Leu	Gly	Lys	Ala	Gly	Gln	Gly	Lys	Ser	Tyr	Trp	Ala	Gly	Ala	
				420					425					430			
65	Val	Ser	Arg	Ala	Trp	Ala	Cys	Gly	Arg	Leu	Pro	Gln	Tyr	Asp	Phe	Val	
			435					440					445				
70	Phe	Ser	Val	Pro	Cys	His	Cys	Leu	Asn	Arg	Pro	Gly	Asp	Ala	Tyr	Gly	
		450					455					460					
75	Leu	Gln	Asp	Leu	Leu	Phe	Ser	Leu	Gly	Pro	Gln	Pro	Leu	Val	Ala	Ala	
		465				470					475					480	
80	Asp	Glu	Val	Phe	Ser	His	Ile	Leu	Lys	Arg	Pro	Asp	Arg	Val	Leu	Leu	
					485					490					495		
85	Ile	Leu	Asp	Gly	Phe	Glu	Glu	Leu	Glu	Ala	Gln	Asp	Gly	Phe	Leu	His	
				500					505					510			
90	Ser	Thr	Cys	Gly	Pro	Ala	Pro	Ala	Glu	Pro	Cys	Ser	Leu	Arg	Gly	Leu	
			515					520					525				

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	Leu	Ala	Gly	Leu	Phe	Gln	Lys	Lys	Leu	Leu	Arg	Gly	Cys	Thr	Leu	Leu	
	530						535					540					
5	Leu	Thr	Ala	Arg	Pro	Arg	Gly	Arg	Leu	Val	Gln	Ser	Leu	Ser	Lys	Ala	
	545					550					555					560	
10	Asp	Ala	Leu	Phe	Glu	Leu	Ser	Gly	Phe	Ser	Met	Glu	Gln	Ala	Gln	Ala	
					565					570					575		
15	Tyr	Val	Met	Arg	Tyr	Phe	Glu	Ser	Ser	Gly	Met	Thr	Glu	His	Gln	Asp	
				580					585					590			
20	Arg	Ala	Leu	Thr	Leu	Leu	Arg	Asp	Arg	Pro	Leu	Leu	Leu	Ser	His	Ser	
				595				600						605			
25	His	Ser	Pro	Thr	Leu	Cys	Arg	Ala	Val	Cys	Gln	Leu	Ser	Glu	Ala	Leu	
		610					615					620					
30	Leu	Glu	Leu	Gly	Glu	Asp	Ala	Lys	Leu	Pro	Ser	Thr	Leu	Thr	Gly	Leu	
	625					630					635					640	
35	Tyr	Val	Gly	Leu	Leu	Gly	Arg	Ala	Ala	Leu	Asp	Ser	Pro	Pro	Gly	Ala	
					645					650					655		
40	Leu	Ala	Glu	Leu	Ala	Lys	Leu	Ala	Trp	Glu	Leu	Gly	Arg	Arg	His	Gln	
				660					665					670			
45	Ser	Thr	Leu	Gln	Glu	Asp	Gln	Phe	Pro	Ser	Ala	Asp	Val	Arg	Thr	Trp	
			675					680					685				
50	Ala	Met	Ala	Lys	Gly	Leu	Val	Gln	His	Pro	Pro	Arg	Ala	Ala	Glu	Ser	
		690					695					700					
55	Glu	Leu	Ala	Phe	Pro	Ser	Phe	Leu	Leu	Gln	Cys	Phe	Leu	Gly	Ala	Leu	
	705					710					715					720	
60	Trp	Leu	Ala	Leu	Ser	Gly	Glu	Ile	Lys	Asp	Lys	Glu	Leu	Pro	Gln	Tyr	
					725					730					735		
65	Leu	Ala	Leu	Thr	Pro	Arg	Lys	Lys	Arg	Pro	Tyr	Asp	Asn	Trp	Leu	Glu	
				740					745					750			
70	Gly	Val	Pro	Arg	Phe	Leu	Ala	Gly	Leu	Ile	Phe	Gln	Pro	Pro	Ala	Arg	
			755					760					765				
75	Cys	Leu	Gly	Ala	Leu	Leu	Gly	Pro	Ser	Ala	Ala	Ala	Ser	Val	Asp	Arg	
		770					775					780					
80	Lys	Gln	Lys	Val	Leu	Ala	Arg	Tyr	Leu	Lys	Arg	Leu	Gln	Pro	Gly	Thr	
	785					790					795					800	
85	Leu	Arg	Ala	Arg	Gln	Leu	Leu	Glu	Leu	Leu	His	Cys	Ala	His	Glu	Ala	
					805					810					815		
90	Glu	Glu	Ala	Gly	Ile	Trp	Gln	His	Val	Val	Gln	Glu	Leu	Pro	Gly	Arg	
				820					825					830			

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Leu Ser Phe Leu Gly Thr Arg Leu Thr Pro Pro Asp Ala His Val Leu
835 840 845

5 Gly Lys Ala Leu Glu Ala Ala Gly Gln Asp Phe Ser Leu Asp Leu Arg
850 855 860

10 Ser Thr Gly Ile Cys Pro Ser Gly Leu Gly Ser Leu Val Gly Leu Ser
865 870 875 880

15 Cys Val Thr Arg Phe Arg Ala Ala Leu Ser Asp Thr Val Ala Leu Trp
885 890 895

20 Glu Ser Leu Gln Gln His Gly Glu Thr Lys Leu Leu Gln Ala Ala Glu
900 905 910

Glu Lys Phe Thr Ile Glu Pro Phe Lys Ala Lys Ser Leu Lys Asp Val
915 920 925

25 Glu Asp Leu Gly Lys Leu Val Gln Thr Gln Arg Thr Arg Ser Ser Ser
930 935 940

30 Glu Asp Thr Ala Gly Glu Leu Pro Ala Val Arg Asp Leu Lys Lys Leu
945 950 955 960

35 Glu Phe Ala Leu Gly Pro Val Ser Gly Pro Gln Ala Phe Pro Lys Leu
965 970 975

Val Arg Ile Leu Thr Ala Phe Ser Ser Leu Gln His Leu Asp Leu Asp
980 985 990

40 Ala Leu Ser Glu Asn Lys Ile Gly Asp Glu Gly Val Ser Gln Leu Ser
995 1000 1005

45 Ala Thr Phe Pro Gln Leu Lys Ser Leu Glu Thr Leu Asn Leu Ser
1010 1015 1020

50 Gln Asn Asn Ile Thr Asp Leu Gly Ala Tyr Lys Leu Ala Glu Ala
1025 1030 1035

55 Leu Pro Ser Leu Ala Ala Ser Leu Leu Arg Leu Ser Leu Tyr Asn
1040 1045 1050

Asn Cys Ile Cys Asp Val Gly Ala Glu Ser Leu Ala Arg Val Leu
1055 1060 1065

60 Pro Asp Met Val Ser Leu Arg Val Met Asp Val Gln Tyr Asn Lys
1070 1075 1080

65 Phe Thr Ala Ala Gly Ala Gln Gln Leu Ala Ala Ser Leu Arg Arg
1085 1090 1095

70 Cys Pro His Val Glu Thr Leu Ala Met Trp Thr Pro Thr Ile Pro
1100 1105 1110

75 Phe Ser Val Gln Glu His Leu Gln Gln Gln Asp Ser Arg Ile Ser
1115 1120 1125

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Leu Arg
1130

5 <210> 96
<211> 17
<212> PRT
<213> Human herpesvirus

10 <400> 96
Tyr Leu Gln Gln Asn Trp Trp Thr Leu Leu Val Asp Leu Leu Trp Leu
1 5 10 15

15 Leu

20 <210> 97
<211> 16
<212> PRT
<213> Homo sapiens

25 <400> 97
Ile Gly His Val Tyr Ile Phe Ala Thr Cys Leu Gly Leu Ser Tyr Asp
1 5 10 15

30 <210> 98
<211> 8
<212> PRT
<213> Mycoplasma penetrans

35 <400> 98
Ile Tyr Ile Phe Ala Ala Cys Leu
1 5

40 <210> 99
<211> 15
<212> PRT
<213> Unknown

45 <220>
<223> Description of Unknown: Six-transmembrane
epithelial antigen of prostate peptide

50 <400> 99
His Gln Gln Tyr Phe Tyr Lys Ile Pro Ile Leu Val Ile Asn Lys
1 5 10 15

55 <210> 100
<211> 15
<212> PRT
<213> Unknown

60 <220>
<223> Description of Unknown: Six-transmembrane
epithelial antigen of prostate peptide

65 <400> 100
Leu Leu Asn Trp Ala Tyr Gln Gln Val Gln Gln Asn Lys Glu Asp
1 5 10 15

70 <210> 101
<211> 14
<212> PRT
<213> Homo sapiens

75 <400> 101
Glu Phe His Ala Cys Trp Pro Ala Phe Thr Val Leu Gly Glu
1 5 10

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5<210> 102<211> 15<212> PRT<213> Homo sapiens

10<400> 102Trp Gln Pro Phe Leu Lys Asp His Arg Ile Ser Thr Phe Lys Asn15151015

15<210> 103<211> 15<212> PRT<213> Human papillomavirus

20<400> 103Leu Phe Val Val Tyr Arg Asp Ser Ile Pro His Ala Ala Cys His1551015

25<210> 104<211> 15<212> PRT<213> Human papillomavirus

30<400> 104Gly Leu Tyr Asn Leu Leu Ile Arg Cys Leu Arg Cys Gln Lys Pro1551015

35<210> 105<211> 13<212> PRT<213> Homo sapiens

40<400> 105Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro15510

45<210> 106<211> 25<212> PRT<213> Mycobacterium tuberculosis

50<400> 106Phe Ser Lys Leu Pro Ala Ser Thr Ile Asp Glu Leu Lys Thr Asn Ser1551015

Ser Leu Leu Thr Ser Ile Leu Thr Tyr2025

55<210> 107<211> 28<212> PRT<213> Mycobacterium tuberculosis

60<400> 107Gly Asn Ala Asp Val Val Cys Gly Gly Val Ser Thr Ala Asn Ala Thr1551015

65Val Tyr Met Ile Asp Ser Val Leu Met Pro Pro Ala2025

70<210> 108<211> 13<212> PRT<213> Homo sapiens

75<400> 108Gly Ser Pro Tyr Val Ser Arg Leu Leu Gly Ile Cys Leu

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<213> Clostridium tetani

<400> 115

5 Gln Tyr Ile Lys Ala Asn Ser Lys Phe Ile Gly Ile Thr Glu
1 5 10

<210> 116

10 <211> 20

<212> PRT

<213> Hepatitis B virus

<400> 116

15 Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu Leu
1 5 10 15

Met Thr Leu Ala

20 20

<210> 117

<211> 13

25 <212> PRT

<213> Influenza A virus

<400> 117

30 Pro Lys Tyr Val Lys Gln Asn Thr Leu Lys Leu Ala Thr
1 5 10

<210> 118

<211> 15

35 <212> PRT

<213> Hepatitis B virus

<400> 118

40 Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp
1 5 10 15

<210> 119

<211> 16

45 <212> PRT

<213> Influenza A virus

<400> 119

50 Tyr Ser Gly Pro Leu Lys Ala Glu Ile Ala Gln Arg Leu Glu Asp Val
1 5 10 15

<210> 120

<211> 18

55 <212> PRT

<213> Plasmodium falciparum

<400> 120

60 Glu Lys Lys Ile Ala Lys Met Glu Lys Ala Ser Ser Val Phe Asn Val
1 5 10 15

Val Asn

65

<210> 121

<211> 4

<212> PRT

70 <213> Human papillomavirus

<400> 121

Gln Asp Lys Leu
1

75

<210> 122

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<211> 8
<212> PRT
<213> Artificial Sequence

5 <220>
<223> Description of Artificial Sequence: Synthetic peptide

10 <400> 122
Val Tyr Asp Phe Phe Val Trp Leu
1 5

15 <210> 123
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<212> DNA
<213> Artificial Sequence

20 <220>
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25 <400> 123
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30 <210> 124
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35 <220>
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40 <210> 125
<211> 30
<212> DNA
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45 <220>
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50 <400> 125
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55 <210> 126
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<212> DNA
<213> Artificial Sequence

60 <220>
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65 <210> 127
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<212> DNA
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70 <220>
<223> Description of Artificial Sequence: Synthetic primer

75 <400> 127
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5

<210> 128
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

10

15

<400> 128
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42

20

<210> 129
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

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39

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<210> 130
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

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<400> 130
aaatctagaa tggcggcccc cggcgcccc

29

45

<210> 131
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

50

<400> 131
ggggaattct agatcctcaa agagtgtg

29

55

<210> 132
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<212> DNA
<213> Artificial Sequence

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60

65

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48

70

<210> 133
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic oligonucleotide

75

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5	<210> 134 <211> 69 <212> DNA <213> Artificial Sequence	
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	ttgatcccc	69
20	<210> 135 <211> 29 <212> DNA <213> Artificial Sequence	
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30	<400> 135 tttgatccc tagatgtct gatagccgg	29
35	<210> 136 <211> 9 <212> PRT <213> Human papillomavirus	
40	<400> 136 Arg Ala His Tyr Asn Ile Val Thr Phe 1 5	
45	<210> 137 <211> 17 <212> PRT <213> Gallus gallus	
50	<400> 137 Ile Ser Gln Ala Val His Ala Ala His Ala Glu Ile Asn Glu Ala Gly 1 5 10 15	
55	Arg	
60	<210> 138 <211> 8 <212> PRT <213> Human papillomavirus	
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