A Phase 1 Study of a Recombinant Viruslike Particle Vaccine against Human Papillomavirus Type 11 in Healthy Adult Volunteers

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Viruslike particles (VLPs) produced from the L1 protein of several papillomaviruses have induced protection from infection after live challenge in animal models. In the present study, the safety and immunogenicity of a human papillomavirus (HPV)-11 L1 VLP candidate vaccine were measured in a phase 1, dose-finding trial in humans. The vaccine was well tolerated and induced high levels of both binding and neutralizing antibodies. Marked increases in lymphoproliferation to HPV-11 L1 antigens were noted after the second vaccination. In addition, lymphoproliferation was induced after vaccination in peripheral blood mononuclear cells (PBMC) stimulated with heterologous L1 VLP antigens of HPV types 6 and 16. Statistically significant increases in HPV antigen–specific interferon–γ and interleukin-5 production were measured from PBMC culture supernatants. This candidate HPV VLP vaccine induced robust B and T cell responses, and T cell helper epitopes appear to be conserved across HPV types.

Human papillomaviruses (HPVs) infect epithelial tissues of skin and mucous membranes. More than 30 different HPV types infect the genital tract, producing anogenital warts and a variety of benign and malignant neoplasms, including cervical cancer [1, 2]. Treatment of these extraordinarily common sexually transmitted diseases (STDs) consists primarily of ablation or removal of infected tissues, although antiviral and immunomodulatory drugs have also been shown to have some therapeutic benefit [3, 4]. All modes of therapy are associated with significant rates of failure and relapse, and some have significant toxicity. Prevention of HPV infections consists primarily of avoiding contact with infectious lesions, although barrier methods of contraception may offer some protection [5, 6]. Widespread infection and serious disease, as well as inadequate modes of therapy and prevention, have led to interest in the development of HPV vaccines.

Because HPVs are exquisitely species-specific and have not been propagated in tissue culture, significant amounts of well-characterized HPV antigens have not been widely available. Few immunologic studies have been performed with uniform antigen preparations, and immune correlates of disease resolution and prevention from infection have not been established. However, in recent years, several groups have recognized that viruslike particles (VLPs) closely approximate the antigenic characteristics of wild-type virions [7–15]. HPV VLPs derived from expression in eucaryotic cells of the major capsid protein L1 can be used to detect antibodies in the serum of infected patients and to induce the production of neutralizing antibodies in laboratory animals. In addition, studies conducted in animal models have demonstrated that VLP vaccines can induce an effective immune response. Studies in the cow, rabbit, and dog all have shown that vaccination with homologous VLPs can protect from live virus challenge [16–18].

In the present study, we administered an HPV type 11 (HPV-11) VLP candidate vaccine to 65 healthy adults without serologic evidence of previous HPV-11 infection. The purpose of the study was to evaluate the tolerability, safety, and antigenicity of the vaccine. Antigenicity was assessed by measuring binding and neutralizing antibodies and by determining proliferative and cytokine responses of PBMC after in vitro stimulation, using 1 L1 VLPs from the homologous HPV type (HPV-11) and from 3 heterologous types (HPV-6, -16, and -18).

Subjects and Methods

Study Subjects

All subjects were enrolled at the University of Rochester Vaccine Center. Subjects were adults between the ages of 18 and 45 years...
and were healthy, as determined by medical history; physical examination, including genital examination and pelvic examination for women; electrocardiogram; and routine laboratory tests. Laboratory criteria for eligibility included hemoglobin level >11 g/dL, white blood cell count >4000 cells/mm³, platelet count >120,000 cells/mm³, normal urinalysis findings, and aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, calcium, phosphorus, total protein, albumin, serum electrolytes, glucose, blood urea nitrogen, and creatinine values within the normal range.

Criteria for exclusion included abnormal serum immunoglobulin G, A, or M level; positive urine pregnancy test or abnormal Pap smear for women; any acute or chronic condition limiting the volunteer’s ability to complete the study; a history or clinical manifestation of significant metabolic, pulmonary, cardiovascular, hematologic, gastrointestinal, dermatologic, or genitourinary disease; a history of cancer or chronic hepatitis; a history of alcohol or other drug abuse within 2 years of enrollment; current use of immunosuppressive medications; a history of immunodeficiency; receipt of immunoglobulin or blood products within 4 months of study entry; anogenital warts within the previous year; serum antibodies to hepatitis C, hepatitis B surface antigen, or human immunodeficiency virus (HIV) type 1; and positive urine test results for drugs of abuse or a positive blood alcohol level. Before enrollment, all subjects had negative HPV-11 ELISA tests, as described below.

Study Design

This was a blinded, randomized, placebo-controlled dose escalation study. The VLPs in the vaccine preparation were formed by self-assembly of HPV L1 capsid protein produced by baculovirus vectors in Tricholusia ni [19–21]. The HPV-11 L1 VLP vaccine is referred to as “MEDI-501” (MedImmune). Either MEDI-501 formulated in aluminum hydroxide or an alum adjuvant control containing no protein was administered to 12 vaccine recipients and 4 placebo recipients in each of the 4 dosing groups (2.8 μg, 9.4 μg, 31.3 μg, and 104.3 μg, referred to hereafter as the 3, 9, 30, and 100 μg doses). Sequential eligible volunteers were randomized within each treatment group by a computer-generated scheme to receive either vaccine or adjuvant control, in a 3:1 ratio. Immunizations were administered intramuscularly in the deltoid at 0, 4, and 16 weeks. Subjects were seen and evaluated before and after each injection and at weeks 12, 24, and 48 after initial vaccination. Evaluations consisted of a medical history, physical examination, and performance of routine laboratory tests, as outlined above.

Serologic and Virologic Studies

ELISA tests. HPV-11 L1 VLPs were diluted in PBS and were bound to 96-well polystyrene plates by incubation at 37°C for 1 h. Plates were washed 4 times with PBS containing 5% nonfat dry milk. After a 1-h incubation at room temperature, the plates were washed 4 times with PBS-Tween. Human serum samples were diluted in PBS containing 1% nonfat dry milk and were added to the plates for a 2-h incubation at room temperature. After further washing, VLP-specific antibodies were identified, using peroxidase-labeled anti-human IgG. After a 1-h incubation at room temperature, the plates were washed, and peroxidase substrate was added to the wells. Optical density readings were taken 30 min after the addition of substrate.

Neutralization tests. An in vitro reverse-transcriptase-polymerase chain reaction (RT-PCR)–based assay, originally described by Smith et al. [22], was used to detect neutralizing antibodies against HPV-11. HaCaT cells, an aneuploid human keratinocyte cell line [23], were grown to 85%–100% confluency in 24 well plates. HPV-11 particles obtained from xenograft propagation were preincubated with dilutions of serum samples at 35°C for 75 min and were added to the HaCaT cells [24]. Six days after infection, total RNA was harvested from the cells, and 10% of the total RNA was used for cDNA synthesis, using an oligo d-T primer. Ten percent of the cDNA was then used as a template for nested RT-PCR, using primers specific for the E1+E4 spliced message. RT-PCR products were separated on an agarose gel and were visualized by ethidium bromide staining. Absence of the E1+E4 band indicated that viral neutralization had occurred. Neutralization titer was defined as the highest serum dilution that inhibited the synthesis of the E1+E4 spliced message. As a control for RNA isolation, amplification of β-actin–specific DNA was performed on all cDNA samples found to be E1+E4 negative. To control for specificity and virus infection, amplification with E1+E4–specific primers was carried out with cDNA prepared from uninfected HaCaT cells, cells infected with HPV-11 that had not been preincubated with serum, and cells infected with HPV-11 that had been preincubated with a seronegative human control serum.

Lymphoproliferative assays (LPAs). L1 VLPs corresponding to HPV-6, -11, -16, and -18 and to parvovirus B19 VP2 were produced at MedImmune, using the baculovirus expression system. Purification was accomplished by cesium chloride and sucrose gradient centrifugation and by phenyl hydrophobic interaction chromatography. The final bulk product was dialyzed and sterilized by filtration. Phytohemagglutinin was purchased from Sigma, and tetanus toxoid from Connaught Laboratories. LPAs were conducted by using PBMC that were drawn on days 0, 42 (2 weeks after the second vaccination), and 126 (4 weeks after the third and final vaccination). Separation, cryopreservation, and thawing of PBMC followed consensus techniques used in our laboratories that have been established by the National Institutes of Health AIDS Vaccine Evaluation Group and the AIDS Clinical Trials Group [25]. All assays were conducted after all PBMC were collected and were performed without knowledge of treatment assignment (vaccine or placebo). In brief, 10⁶ PBMC per well were incubated in round-bottom plates for 6 days with medium or antigen in quadruplicate, in RPMI 10% heat-inactivated autologous serum (drawn before vaccination). For the 2 lower vaccine doses (3 and 9 μg, also referred to as the low-dose group), the HPV antigens were used in vitro at final concentrations of 2 and 10 μg/mL, respectively. For the 2 higher vaccine dose groups (30 and 100 μg, also referred to as the high-dose group), the HPV antigens were limited in supply and were used in vitro at 1 and 5 μg/mL, respectively. The concentrations of other antigens used were 5 lytic-forming units/mL for tetanus and 5 μg/mL for the B19 baculovirus control. The B19 control was available in sufficient quantity only to perform assays on the first 3 vaccine dose groups. On the sixth day of incubation, 50 μL of media was removed from each well, 50 μL of tritiated
thymidine (1 μCu) was added, and the plates were harvested and were read the following morning on a Packard Instrument Top-Count. The stimulation index (SI) was calculated as the mean antigen stimulation/mean medium stimulation.

Cytokine assay. The 50 μL samples from the 4 replicate wells for each condition, which were removed on the sixth day, were pooled and were stored at −70°C until use. At that time, the interleukin (IL)−5 and interferon (INF)−γ concentrations of the samples were determined by ELISA, using antibody pairs obtained from Pharmingen, as described elsewhere [26]. Assays were performed in duplicate. The lower limit of sensitivity for each assay was 50 pg/mL.

Statistical Methods

This phase 1 trial was designed to obtain safety and immunogenicity information and not to test for efficacy differences among treatment groups. Summary and descriptive statistics and graphs were used to describe results across treatment groups. All volunteers who received study vaccine were included in analyses of safety. Adverse events that occurred or worsened within 8 weeks after the last scheduled administration of study medication were assessed blindly for severity and relationship to study drug. Volunteers were considered to be evaluable for immunogenicity if they received an immunization and were followed up for ≥3 weeks. Neutralizing antibody studies were performed only for volunteers who received all 3 injections of study medication.

In the LPA analysis, assays in which none of the control antigens or mitogens revealed an SI >3.0 were considered to have nonviable T cells and were removed from the analysis before unblinding. The assay results for the VLP recipients are presented in tables and figures as the overall responses in each vaccine dose group. However, for our formal statistical analysis, we retained only the data from those patients who had observations at all time points. Because of missing observations and the use of smaller amounts of VLPs in some assays with the 30 and 100 μg dosing groups, the formal statistical analysis was confined to the lower-dose groups (3 and 9 μg) and their matching control groups. Given the reduced data set, we sought to determine simply whether there were differences in lymphoproliferative response, or in the production of INF−γ or IL−5, before and after immunization and between the placebo and MEDI-501 recipients, regardless of dose. The data were analyzed by a 2-way analysis of variance (ANOVA), with vaccination (MEDI-501 vs. placebo) treated as a between-groups variable and time of PBMC collection (before vs. after immunization) treated as a within-subjects variable. A statistically significant interaction between these 2 variables meant that a response after vaccination noted only in the MEDI-501 recipients could be attributed to the vaccine. Two-sided P values ≤.05 were considered to be statistically significant.

Results

Characteristics of Study Participants

A total of 65 volunteers were enrolled. The mean age of study participants was ∼30 years, with a range of 19−45 years. Twenty-four volunteers (37%) were men, and 41 (63%) were women. Sixty (92%) were white, 2 were African American, 1 was Latino, and 2 were members of other racial groups. In general, study subjects were at low risk for acquiring STDs. Fifty-three (82%) had one or no sex partner during the year before enrollment; 10 had 2 partners in the past 12 months, and 1 each had 3 and 5 partners during that period. Few of the participants had histories of previous STDs. A history of chlamydial infection was obtained from 8 patients, 3 had histories of genital herpes, and 1 each had had gonorrhea and anogenital warts.

Sixteen subjects were enrolled in each of groups A, B, C, and D. An additional subject was enrolled in group D when a volunteer who was randomized to the vaccine arm became permanently unavailable for follow-up after moving out of the country after receipt of only the initial vaccination. Three subjects in group A (2 in the vaccine arm and 1 in the adjuvant control arm) received only 2 doses. One vaccine recipient was noncompliant, and another developed hives after the second injection, which were believed by the clinical staff to be possibly related to study medication. The study team decided not to administer a second booster injection to that individual. The adjuvant control recipient became pregnant and was not given the third injection. Two subjects in the highest-dose group (both in the vaccine arm) received only 2 injections. One volunteer was noncompliant, and the second moved out of town and refused further study participation. Overall, 59 (91%) of the 65 study participants received all 3 scheduled doses of study medication.

Clinical and Laboratory Toxicity

Study medications were well tolerated. No changes in vital signs were associated with vaccine administration. Pain within 4 days after injection was the most frequently observed adverse event and occurred after 72% (136/188) of immunizations (after 73% of active vaccine injections and after 70% of adjuvant control injections). Only 1 volunteer, an adjuvant control recipient, had an episode of severe pain. This episode occurred after the primary immunization, resolved within 72 h, and did not recur after the 2 booster vaccinations. Frequencies of other injection site adverse events ( bruising, induration, inflammation, and edema) did not vary significantly among the treatment groups.

Headache was reported more frequently within 4 days after an injection of vaccine than after an injection of adjuvant control (31% vs. 4%). Frequency of headaches did not vary among vaccine groups, and headaches were always of mild or moderate severity. Six volunteers reported rash and/or pruritis that was judged by the clinical investigator to be related to study vaccine. Five received MEDI-501, and one received adjuvant control. In 4 of these volunteers, rashes or pruritis developed within 4 days of the study vaccine injection. In all but 1 volunteer, these manifestations were mild to moderate in severity and did not recur with subsequent injections. As described above, 1 vol-
 Immunologic Studies

Serology. Administration of each of the 4 doses of MEDI-501 vaccine produced dramatic increases in serum antibodies, as measured by ELISA (figure 1). Geometric mean titers (GMTs) 4 weeks after the initial vaccination ranged from a low of 34 in the 3 μg arm to 449 in the 100 μg arm. Four weeks after the first dose, GMT measurements ranged from 1324 to 2016. An additional increase was noted after the second booster, which produced GMT values 4 weeks later of 2786–6400. Thus, a clear dose response curve was generated, although differences among values measured in the 9, 30, and 100 μg groups were not readily apparent after 1 week following the first booster. ELISA titers decreased by about 0.5 log10 between weeks 20 and 48 of study.

Serum HPV-11 neutralizing antibody titers were measured in all patients before vaccination and among patients receiving all 3 injections at weeks 20 and 48 (table 1). No subject had serum neutralizing activity before vaccination, and GMT values at week 20 were similar among the 9, 30, and 100 μg groups. Among subjects who received all 3 injections, 7 of 10 subjects in the 3 μg arm had titers >1000, whereas 10 of 10 subjects in the 100 μg arm had neutralizing antibody titers of that magnitude. As was noted for antibodies measured by ELISA, neutralization antibody titers decreased by about 0.5 log10 by week 48 (data not shown).

Lymphoproliferation. The overall data for these LPA studies are summarized in table 2. The placebo patients from each group (n = 4) are summed, to make a total of 16 control recipients. The responses of the others are shown by the vaccine dose group for days 0, 42, and 126. Proliferative responses to HPV antigens were found to be independent of the VLP vaccine dose. This is graphically illustrated by the response to high-dose in vitro HPV-11 antigen stimulation (figure 2). However, proliferation to the tetanus control was lower in the 100 μg MEDI-501 group, suggesting that the cells for the assays may not have been equivalently viable and responsive.

Due to the dose independence, data from all MEDI-501 recipients were combined to compare with those from placebo recipients (figure 3). There was a substantial increase due to vaccination after all HPV antigen stimulations, when results in the placebo group are compared with results in the vaccine group. No SI increases were observed in response to any antigen in the placebo group. The statistical analysis done on the matched data sets showed no statistically significant increase between baseline and the later time points in proliferation to either tetanus (P = .49) or parvovirus (P = .26). In contrast, such an interaction was present for the high-dose HPV-11 antigen (P = .04). A trend was also present for the 10 μg HPV-6 antigen stimulation (P = .09), which shares 93% amino acid homology in the L1 gene, and for the HPV-16 high-dose stimulation (P = .06), which shares 68% homology.

Many individuals had baseline responses >3.0 (table 2). Whether these were due to prior exposure to HPV, to a cross-reacting antigen in the VLP preparation, or to proliferation due to baculovirus contamination was not ascertained. Similar background responses to baculovirus preparations have been seen in trials in which baculovirus-derived antigens were used for proliferation studies (data not shown).

When it became clear that T cell responses had developed not only to the VLP-11 antigen, but also possibly to VLPs of other HPV types (HPV-6 and -16), a decision was made to test more purified antigen preparations, to decrease the likelihood that the responses were due to baculovirus contamination. A new set of L1 VLP antigens for LPA was purified by using chromatography and filtration after isolation of VLPs by cesium and sucrose gradients. A comparison of proliferation between the original and more purified VLP preparations was performed, using cells from 4 volunteers in the 30 μg dose group, and showed no difference between the original and more purified antigens (data not shown).

![Figure 1. Seroreactivities toward human papillomavirus (HPV)-11 L1 viruslike particle (VLP) vaccine of vaccinated subjects over time and according to vaccine dose. The placebo recipients tested negative before and after immunization (not shown).](https://academic.oup.com/jid/article-abstract/183/10/1485/892391)
Cytokine analysis. INF-γ and IL-5, which were secreted during the lymphoproliferation cultures, were measured in supernatants obtained after 144 h of in vitro stimulation. The mean cytokine levels for each of the groups are presented in table 3. Once again, the data have been combined across all vaccine dosing groups, as no statistical difference was observed for any 1 group. There were substantial increases in cytokine production in response to most of the HPV antigen stimulations. By ANOVA, these increases in INF-γ production over time in the vaccine recipients were significant in comparison with the response of placebo recipients for the HPV-11 high-dose in vitro stimulation (P = .006), with a trend toward significance for high-dose HPV-16 (P = .08). No significant interaction effect was observed with the parvovirus B19 (P = .50) or tetanus antigen (P = .17) stimulation in the same volunteers.

The analysis of the IL-5 data also revealed HPV-specific stimulation induced by vaccination for this Th2-phenotypic cytokine (table 2). Again, no significant increase was seen in MEDI-501 recipients, compared with the placebo control recipients, when their PBMC were stimulated with either tetanus (P = .31) or parvovirus B19 VLPs (P = .55). However, increases were seen in response to the high-dose HPV-11 in vitro stimulation (P = .05).

Discussion

This study presents the results of an HPV VLP vaccine preparation to be administered to humans. We observed that VLP vaccines induce robust B and T cell responses in humans and that such responses are partially conserved across clinically and serologically distinct HPV types. The results demonstrate clearly that this HPV 11 preparation, formulated in an aluminum hydroxide adjuvant, is safe, well tolerated, and highly immunogenic in healthy seronegative volunteers. At doses of ∼3, 9, 30, and 100 μg, all volunteers briskly produced antibody, as measured by ELISA. There was an obvious dose response relationship, although no significant differences were observed among the recipients of the 3 higher doses. In addition, high levels of serum neutralizing antibody were produced. All study volunteers who received 3 doses of MEDI-501 at a dose of ≥9 μg achieved serum neutralizing antibody titers of ≥1000. Both binding and neutralizing antibodies remained high at 48 weeks after initial vaccination.

We also observed that the MEDI-501 vaccine induced T cell proliferation and cytokine production. Epidemiologic observations point to a role for cell-mediated immune mechanisms in the control of HPV infections, including anogenital warts (condylomata acuminata). A marked lymphocyte and macrophage infiltrate consistent with a delayed-type hypersensitivity reaction is present in naturally regressing condylomata acuminata and exhibits an increase in the CD4+:CD8+ ratio and expression of lymphocyte activation markers [27, 28]. Patients with HIV infection have a 2–7-fold increased prevalence of condylomata acuminata, compared with noninfected control subjects [29, 30].

T cell responses to natural HPV infection have been difficult to measure [31] (and present authors’ unpublished data). The SIs induced by the MEDI-501 vaccine were far higher than those reported in natural HPV infections and were especially noteworthy in view of the fact that these assays were conducted...
Figure 2. Stimulation indices (mean ± SEM) for volunteers studied from each vaccine dose group after in vitro stimulation with human papillomavirus (HPV)-11 virusslike particle (VLP) vaccine. The 3 µg \((n = 7)\) and 9 µg \((n = 11)\) dose groups were stimulated with 10 µg/mL of VLP vaccine in vitro, and the higher-dose groups \((n = 12\) for 30 µg and \(n = 13\) for 100 µg) were stimulated with 5 µg/mL of VLP vaccine in vitro. The placebo recipients from each group \(4\) per group) were stimulated with similar amounts of antigen.

Figure 3. Stimulation indices (mean ± SEM) for each human papillomavirus antigen stimulation are shown over time with placebo volunteer values pooled and vaccinees from all 4 dosing groups similarly pooled. Results are shown for the higher dose of the preparation for each antigen used for in vitro stimulations.
Viruslike particle vaccine recipients increase in proliferation to B19 VLP control, which suggests that can't differences in responses between infected individuals and these responses may have been due to prior T cell activation. prior HPV infection. Many adults have serological evidence of did not establish whether this was due to small amounts of VLP antigens that were above a standard SI cutoff of 3.0. We response may have played a protective role [41]. HPV-specific T cell IL-2 production has likewise been observed to decrease with measured in control subjects, which suggests that the T cell re-

consistent with a Th1 profile. In P. S. Shepherd's studies, Th1

associated with the secretion of both INF-\(\gamma\) and IL-2, a similar rate was noted among recipients of the adjuvant control, and all episodes of pain, except one that occurred in an adjuvant control recipient, were mild or moderate in nature and resolved within 72 h. This rate and severity of pain are typical of commonly used vaccine preparations administered in alum adjuvants. Of interest was the observation of headache more commonly among MEDI-501 recipients than among adjuvant control recipients. The headache was unrelated to vaccine dose, was of only mild to moderate severity, and resolved in all subjects within 72 h. We have no explanation for our observation of a higher rate of mild to moderate headaches among vaccine recipients.

Rash and/or pruritis was observed in 6 study participants. In 1 individual, hives were noted, and this reaction was believed by the investigators to be potentially related to the vaccine. This individual received no additional vaccine injections. Other study subjects with complaints of rash and/or pruritis received additional injections without adverse consequences. Results of routine complete blood cell counts, serum chemistry studies, and urinalyses were unremarkable and did not demonstrate significant differences among treatment groups or significant changes over time in any treatment group.

Table 3. Cytokine values in 6-day culture supernatants.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Placebo recipients</th>
<th>Viralike particle vaccine recipients</th>
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<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 126</td>
</tr>
<tr>
<td>Interleukin-(\gamma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>231 ± 66 (7/12)</td>
<td>669 ± 253 (7/11)</td>
</tr>
<tr>
<td>HPV-11 low</td>
<td>274 ± 137 (5/10)</td>
<td>500 ± 332 (2/10)</td>
</tr>
<tr>
<td>HPV-6 low</td>
<td>82 ± 35 (4/11)</td>
<td>413 ± 305 (3/8)</td>
</tr>
<tr>
<td>HPV-16 high</td>
<td>17 ± 17 (4/12)</td>
<td>465 ± 439 (2/11)</td>
</tr>
<tr>
<td>HPV-16 low</td>
<td>84 ± 45 (4/9)</td>
<td>514 ± 388 (3/7)</td>
</tr>
<tr>
<td>HPV-18 high</td>
<td>452 ± 394 (3/11)</td>
<td>208 ± 138 (29)</td>
</tr>
<tr>
<td>HPV-18 low</td>
<td>19 ± 13 (29)</td>
<td>665 ± 634 (26)</td>
</tr>
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| NOTE. Data are mean cytokine level ± SEM, in pg/mL (no. of assays with cytokine level >50 pg per mL/total no. of assays). High, high-dose group (5 and 10 ng of antigen); low, low-dose group (1 and 2 ng of antigen).
In addition to establishing the safety and immunogenicity of MEDI-501, this study provides information that will be useful for designing a variety of subsequent investigations. First, the magnitude of T cell responses in peripheral blood is large enough to be able to compare different adjuvant or antigen strategies. Second, the cells from these studies could serve as useful reagents for mapping epitopes to peptides responsible for proliferation and/or cytokine secretion. These epitopes are likely to be conserved across many of the L1 proteins from different HPV types and could lead to new understandings in HPV vaccine design. Third, the brisk T cell response may enable the assessment of whether CD8+ activity was also induced by the VLP vaccines, as has been observed in animal models [46, 52]. Last, the implication of cross-type HPV responses may indicate that a vaccine against low-oncogenic risk HPV genotypes may provide some protection against high-risk HPV genotypes, and vice versa. Limited epidemiologic data suggest that such cross-protection by HPV types may indeed exist [53–55].

This study demonstrated that HPV L1 VLP vaccines are highly immunogenic and induce brisk B cell and T cell responses. Ultimately, the efficacy of these preparations in the prevention of HPV-associated disease must be determined by an appropriately conducted field trial.

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References