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REVIEW

Viral vector-based therapeutic HPV vaccines

Teng Ji[1,2] · Yuchuan Liu[3] · Yutong Li[3] · Chuanfen Li[3] · Yingyan Han[1,2]

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Abstract
Replication-defective viral vector vaccines have several advantages over conventional subunit vaccines, including potent antibody responses, cellular responses critical for eliminating pathogen-infected cells, and the induction of highly immunogenic and durable immune responses without adjuvants. The Human papillomavirus (HPV), a microorganism with over 200 genotypes, plays a crucial role in inducing human tumors, with the majority of HPV-related malignancies expressing HPV proteins. Tumors associated with HPV infection, most of which result from HPV16 infection, include those affecting the cervix, anus, vagina, penis, vulva, and oropharynx. In recent years, the development of therapeutic HPV vaccines utilizing viral vectors for the treatment of premalignant lesions or tumors caused by HPV infection has experienced rapid growth, with numerous research pipelines currently underway. Simultaneously, screening for optimal antigens requires more basic research and more optimized methods. In terms of preclinical research, we present the various models used to assess vaccine efficacy, highlighting their respective advantages and disadvantages. Further, we present current research status of therapeutic vaccines using HPV viral vectors, especially the indications, initial efficacy, combination drugs, etc. In general, this paper summarizes current viral vector therapeutic HPV vaccines in terms of HPV infection, antigen selection, vectors, efficacy evaluation, and progress in clinical trials.

Keywords Viral vectors; Human papillomavirus; Therapeutic vaccine; HPV-related malignancies

Introduction

Hundreds of types of human papillomavirus (HPV) have been detected, and it is a common sexually transmitted virus that infects the genital areas of men and women, including the skin of the penis, vulva (area outside the vagina), and anus, and the linings of the vagina, cervix, and rectum [1]. Most HPV infections are asymptomatic, and certain high-risk HPV types can lead to cancer. Worldwide, HPV is one of the most prominent infectious agents that cause cancer and is associated with a variety of malignancies, most commonly cervical cancers. Nearly all cervical cancer cases are associated with HPV infection, particularly with high-risk HPV types, especially for HPV16. HPV is also associated with vaginal, penile, anal, and oropharyngeal cancers [2]. According to recent studies, one in five men > 15-years of age are infected with one or more of high-risk HPV genotypes [3]. HPV prophylactic vaccines exhibit excellent immunogenicity and prevent the development of HPV-related precancerous lesions and tumors [4]. There is significant regional variation in global HPV vaccination coverage. HPV vaccine coverage in Australia is among the highest in the world, while many low-and middle-income countries have relatively low coverage. Although 96 countries have included HPV vaccines in the national immunization program, the burden of HPV-related tumors remains heavy in low-and middle-income countries due to slow vaccine promotion, low screening and early diagnosis rates, and limited treatment resources [5].

Teng Ji and Yuchuan Liu have contributed equally to this work.

✉ Yingyan Han
hanyingyan1222@163.com

1 Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

2 Key Laboratory of Cancer Invasion and Metastasis (Ministry of Education), Hubei Key Laboratory of Tumor Invasion and Metastasis, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

3 The Second Clinical Medical College, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

In May 2024, the WHO issued a document clarifying that HPV therapeutic vaccine is an important means to eliminate tumors associated with HPV infection [6]. Partha Basu et al. conducted a meta-analysis of 12 Phase II/III clinical trials of HPV therapeutic vaccines prior to January 31, 2022, a total of 734 women received the HPV therapeutic vaccine for CIN2/3. 414 patients regressed to normal or CIN 1, the overall regression ratio in the vaccine group was 0.54 (95% confidence interval 0.39 to 0.69); while in the five randomized controlled trials, the overall regression ratio of 166 women receiving placebo was 0.27 (95% confidence interval 0.20 to 0.34) [7]. Further, Aida Petca et al. analyzed the clinical trials from January 2018 to January2024 and found that HPV vaccine also had certain therapeutic effects in skin cancer and warts [8]. Of course, there are differences in immunogenicity and efficacy, and although promising, there is still room for improved efficacy [9].

Recombinant viral vectors have been used to deliver antigens from specific pathogens for > 40 years, including adenovirus (ADV), poxvirus, herpes simplex virus (HSV), vesicular stomatitis virus (VSV), lentivirus vectors (LV), cytomegalovirus (CMV), measles virus (MV) and lymphocytic choriomeningitis virus (LCMV) [10]. Viral vectors are designed to deliver antigens to specific cells and tissues. Viral vector vaccines can be further optimized to enhance the expression of transgenes in target cells during antigen delivery. Viral vectors have been used in preclinical and clinical trials as vaccines against various infectious diseases, such as HIV, malaria, Ebola virus, and Covid-19 [11–14]. With the worldwide spread of Covid-19, multiple vaccine platforms, including viral vector vaccines, have flourished. Viral vector-based therapeutic HPV vaccines have also been developed and enter the phase of clinical trials, and several products have recently announced the latest clinical results [15–23]. This paper provides an in-depth understanding of the evolving landscape of HPV vaccine technology, highlighting the vectors employed, the diseases they aim to target, the antigens chosen for optimal immune response, the metrics used to evaluate their effectiveness, and the significant strides made in clinical evaluations.

HPV infection and its association with various cancer types

HPV infection has been firmly established as the primary causative factor in the majority of cervical cancer cases. And, cancers arising from diverse anatomical sites are also associated with HPV, albeit to varying extents. According to the Globocan 2012 and the Cancer Incidence in Five Continents (CI5-X) database, 88% of anal cancer, 78% of vaginal cancer, 50% of penile cancer, 24.9% of vulval cancer and 30.8% of oropharyngeal cancer is attributable to HPV [24]. Until now, a total of 14 HPV genotypes have been rigorously categorized as "high risk," primarily owing to their profoundly elevated potential for inducing carcinogenesis. Among these, HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 have been specifically designated as Group 1 carcinogens by the esteemed International Agency for Research on Cancer (IARC), which underscores their exceptional threat. Additionally, HPV66 and HPV68 are also classified in this high-risk category, further broadening the scope of concern for these potentially hazardous genotypes [25]. In a study conducted in China in 2023, it was uncovered that HPV16, 58, 52, 33, and 31/18 are the foremost high-risk human papillomavirus (hrHPV) prevalent in both the CIN 2 and CIN3 cohorts. Concurrently, the research highlights that the breakdown of CIN1, CIN2, and CIN3 cases associated with solitary HPV16 infection was 22.06% and 46.24% for CIN1 and CIN2, respectively, and a significant 55.21% for CIN3. This underscores the carcinogenicity of HPV16, making it the most formidable hrHPV type in the progression of cervical precancerous conditions and malignant tumors [26]. HPV 16 is also responsible for approximately 50–80% of anogenital cancers, including vaginal, vulval, penile, and anal cancer. Other common HPV types that contribute to these cancers include HPV 33, 31, 18, and others [27–29]. Additionally, in the realm of oropharyngeal cancer, HPV 16 holds the distinction of being the most frequently identified type globally, with HPV 33, 18, 31, and 35 following in its wake [30–32]. It is worth mentioning that globally, HPV-16 is also the most common type of HR-HPV in men at 5%, followed by HPV 51 (3%), HPV 52 (3%), HPV 59 (2%) and HPV 18 (2%) [3]. Thus, HPV 16 remains the most threatening type to human health, and the current HPV therapeutic vaccines primarily target HPV16. However, a clinical trial of VGX3100, a therapeutic vaccine against both HPV16 and HPV18, revealed that persistent lesions may be linked to other HPV infections, indicating that patients may have had mixed infections prior to treatment [33].Therefore, future HPV therapeutic vaccines should aim to cover a broader range of HPV types beyond HPV16.

HPV structural characterization and antigen selection for therapeutic HPV vaccine

HPV also causes anogenital warts and recurrent respiratory papillomatosis. HPV has a circular double-stranded DNA genome approximately 8 kb in size, with early and late regions encoding early (E1, E2, E4, E5, E6, and E7) and late (L1 and L2) proteins, respectively [34]. The late proteins refer to the L1 (55 kDa) and L2 (64–78 kDa) proteins. Each viral capsid consists of 72 L1 pentamers and a small amount of L2 protein. L1, a protein with a molecular weight of approximately 55 kDa, which is the major structural component of the virion, is located in the outer layer of the capsid, and the L1 ORF is the most

conserved region of HPV. Therefore, an ORF similarity of < 60% for L1 is considered to be the basis for traditional HPV serotyping [1]. L2 is located in the inner layer of the capsid and plays several important roles in viral infection. L2 interacts with L1 to promote capsid assembly and stability. Moreover, the L2 protein is involved in viral entry into host cells, introducing the viral genome through mechanisms associated with host cell membrane fusion. Furthermore, both L1 and L2 are antigenic options for prophylactic HPV vaccines [35, 36].

The early HPV proteins include seven proteins, E1-E7. E1 is the largest and most conserved ORF in the HPV genome, encoding 600–650 aa, and is involved in the regulation of viral replication and transcription [37]. The E2 protein enhances viral transcription and stable replication; however, E2 can strongly inhibit the expression of E6 and E7 proteins and induce HPV-positive cell growth arrest and senescence. However, studies have confirmed that E2 alone can induce cellular p53-dependent apoptosis in the absence of the HPV genome [38, 39]. An MVA vector carrying the bovine papillomavirus E2 gene was used for therapy [40]. E4 differs greatly among HPV types and functions in a ligand-like manner. Studies have shown that HPV E4 facilitates E6/E7 viral amplification. E5 is a small, hydrophobic transmembrane protein and is an oncogene [41]. E6 and E7 are the antigens most commonly used in therapeutic vaccines [42]. E6 (150 aa) can degrade p53 to promote cell proliferation, regulate expression of TOLL-like receptor-9 [43]. E6 suppresses the RIG-I-mediated induction of IFN-β, chemokines, and IFN-stimulated genes and mediate immune escape of HPV-infected cells [44]. E7 (100 aa) can degrade Rb and cause tumor cell proliferation [45].

Consistent with the requirements for other tumor vaccines, the requirements for HPV-related tumor vaccines are 1. High or specific expression of the antigenic protein by tumor cells. 2. Proteins can be processed naturally into suitable peptides to present. 3. Peptides have high affinity for MHC molecules 4. Peptide/MHC complexes with responding T-cell TCRs have affinity [46]. Notably, the diversity of HLA (encoding MHC proteins) in the population affects the production of immune responses [47–49]. The most studied proteins are E6 and E7, which have been confirmed to have high cellular immunogenicity and are currently the first choice for HPV-related tumor vaccines. Since E6 and E7 can degrade p53 and Rb, respectively, leading to tumorigenesis, E6 and E7 as antigens are often mutated to disable their tumorigenic capacity [43, 50]. In addition, E2 and E5 have also been found to be expressed by tumors and exhibit good immunogenicity, with the potential to become a vaccine [51–54].

Advantages of viral vector platforms

The use of viral vectors as vaccine platforms can induce innate immune responses without the need for adjuvants. Furthermore, analogous to the natural infection process, the viral vector in the target cells, devoid of any external adjuvants, is capable of eliciting robust humoral and cellular immune responses [55]. After viral infection, target cells activate pathways associated with anti-viral pathways, such as the cGAS-STING pathway, IFN signal channel, TNF signaling pathway, etc. All have synergistic anti-tumor effects [56–58]. Simultaneously, viral infections can enhance the ability of macrophages to phagocytose tumor cells and induce and train macrophage memory cells to strengthen tumor cell surveillance [56, 59]. Natural killer (NK) cells activated by viral vectors are also major anti-tumor cells [60]. Furthermore, viral vectors carry specific antigens that can enable the effective expression of antigens in the human body, promote antigen presentation by host cells, activate dendritic cells (cDCs), and produce strong, sustained cellular immunity to continuously remove target cells, thus becoming the main mechanism of therapeutic vaccines. Memory CD8 + T cells allow the body to prevent disease for a prolonged time [15]. Although humoral immunity involving therapeutic vaccines is not a major part of effectiveness evaluation, an increasing number of studies have found that B cell- and plasma cell-secreted antibodies play important roles in anti-tumor immunity, including antibodies that can activate the classical complement pathway (complement-dependent cytotoxicity, CDC), kill target cells, and activate the participation of Fc receptor antibody-dependent cytotoxic effects (ADCCs) [61].

Replication-defective viral vectors, including adenovirus type 5, adenovirus type 26, ChAdOx1, rhabdoviruses (VSV), flaviviruses (YF117D), arenaviruses, and modified vaccinia Ankara (MVA) have been used as therapeutic vaccines for HPV-related tumors. Due to their replication deficiencies, viral vectors possess extensive clinical epidemiology and clinical trial data, exhibiting favorable safety profiles [62–65]. Adenoviruses (Ads) which is a commonly used vaccine vector exhibit extensive tropism for different cells due to their ability to infect non-dividing and dividing cells, with a low risk of insertional oncogenesis due to their existence as episomes [66]. However, Ad5 neutralizing antibodies are common in the population, which can reduce the effectiveness of such vaccines [67].Thus, rare serotypes, such as Ad26, and non-human adenoviruses, such as ChAdOx1, have been developed. They have low or no seroprevalence in the population but are associated with a very rare clotting disorder, thrombosis, and thrombosis with thrombocytopenia syndrome (TTS) [68].MVA, derived from the vaccinia virus, has a high capacity for transgene insertion and broad tropism for mammalian cells since infection

occurs through passive membrane fusion [69]. The VSV genome is simple and can induce mucosal immunity; however, it has the potential for neurovirulence [70]. Flaviviruses and arenaviruses are emerging vaccine carriers that have been used as Lassa and Ebola virus vaccines [71].

Preclinical evaluation of HPV therapeutic vaccine

Similar to other active immunotherapeutic products, during the preclinical stage, therapeutic HPV vaccines need to be verified using appropriate models, including the induction of appropriate immune responses, cellular and humoral immunity, and killing of tumor cells [72]. Immune responses are often detected in healthy animals, with C57BL/6 and non-human primates (cynomolgus and rhesus macaques) being the most commonly used animal species (Table 1). To evaluate the tumor suppressor effect of vaccines, TC-1 cells expressing HPV16-E6 and—E7 and activated Ras oncogene were used in C57BL-6 mice to analyze the anti-tumor effects and changes in immune cell types in the tumor microenvironment (TME) due to the therapeutic vaccine containing the HPV16 E6/E7 antigen [73]. Additionally, MOC1 cells engineered to express HPV6-E6 were used to evaluate the anti-tumor effects of PRGN-2012 in C57BL/6 mice [15]. There are also other cancer cell lines derived from C57BL/6 mice: C3 cells, generated by immortalization and transfection of mouse embryonic cells, express the complete HPV16 genome [74], and mEER cells, derived from mouse tonsil epithelium, have advantages in terms of better translation toward head and neck squamous cell carcinoma (HNSCC) [75]. However, C57BL/6 mice only express H-2 Kb and H-2Db MHC class I molecules, limiting their repertoire of class I epitopes. Therefore, the development of more applicable animal models to verify vaccine effectiveness has been proposed. Beagle dogs expressing E7/HPV16 transgenes via intramuscular (IM) injection of lentiviral particles have been verified as a potential model for persistent infection [76]. *Macaca Fascicularis* papillomavirus type 3(MfPV3), which is phylogenetically and phenotypically similar to HPV16, is also suitable for macaques persistent genital infections [77]. However, Beagle dogs and macaques are difficult to be tumor-bearing and therefore difficult to evaluate the anti-tumor effect of vaccines. Notably, the SfPV1/rabbit papillomavirus model, which induces infection with long-term persistence and malignant progression of lesions, is suitable for both tumor suppression and persistent infection models [78].

Nevertheless, the utilization of animal models in assessing the efficacy of tumor vaccines cannot overlook species-specific disparities. Consequently, there is an imperative need for the establishment of alternative evaluation systems that better recapitulate human responses. The immunogenicity and tumor suppression effects of vaccines can be demonstrated in humanized mice. However, tumor blast cells necessitate the corresponding HLA molecular transduction and antigen expression for effective treatment [79–81]. In vitro induction tests of human peripheral blood mononuclear cells (PBMCs) can detect vaccine reactivity with a large sample size and conduct in vitro killing testing; however, this cannot mimic vaccine effectiveness tests with complex tumor cell compositions [82]. Organoids can better simulate tumor cell composition and immunosuppressive microenvironment and can be used as supplements to tumor vaccine suppression [83]. However, in vitro test cannot effectively evaluate vaccine doses and procedures. Overall, multiple parallel evaluation strategies for the preclinical evaluation of HPV therapeutic vaccines are recommended, based on the respective defects of each evaluation system.

Current research status of therapeutic vaccines using HPV viral vectors

With the advent of tumor immunotherapy, such as PD-1/PD-L1 inhibitors, Chimeric antigen receptor (CAR)-T cell therapy, tumor-infiltrating lymphocytes (TILs) therapy, T cell receptor-engineered T cells (TCR-T) therapy, and other products, the tumor-killing capacity of tumor-specific T cells in vivo has been further confirmed [84–86]. Tumor vaccines, as therapeutic modalities that effectively activate tumor-reactive T cells throughout the body, have also

Table 1 Commonly Used Animal Models for the Evaluation of HPV therapeutic vaccine

Species	models	HPV type and immunogens	Suit for tumor supression model	Suit for persistent infection model	References
C57BL/6N Mouse	TC-1 cells	HPV16 E6/E7	+	–	[76]
	C3 cells	Full genome HPV16	+	–	[74]
	mEER cells	HPV16 E6/E7	+	–	[75]
Cotton-tail rabbit PV		High risk HPVs	+	+	[78]
Macaca fascicularis PV type 3		HPV16-	–	+	[77]
Beagle dogs		High risk HPVs	–	+	[76]

become the focus of many researchers. The development of a therapeutic vaccine for HPV-related tumors has entered a new stage. This paper summarizes the existing therapeutic vaccines for HPV (Table 2). Based on recent reports, as of March 20, 2024, only TA-HPV, a recombinant vaccinia virus expressing modified HPV-16 and -18 *E6* and *E7* genes and VTP-200, a prime-boost vaccine composed of ChAdOx1-HPV and MVA-HPV, have completed phase II clinical trials. Furthermore, PRGN-2009 was in clinical phase II, whereas Vvax-001 had already entered clinical phase II. However, phase I of Ad-E6E7 and Ad26.HPV18 was terminated due to a low anti-viral potency and low enrollment. None of the other clinical trials entered Phase II.

TA-HPV showed immunogenicity in 29 patients with stage Ib or IIa cervical cancer; eight patients developed HPV-specific serological responses, and four patients developed HPV-specific CTLs after a single vaccination in phase I [16]. TA-HPV combined TA-CIN which is a recombinant fusion protein comprising HPV16- E6/E7/L2, showed significant effects, 9 of 10 women with HPV 16-positive high grade VIN demonstrated HPV 16-specific proliferative T cell and/or serological responses and three patients additionally exhibited lesion shrinkage or symptom relief [87]. A reduction in lesion size was observed in 6 patients (17%) and improved symptom atology in 15 (62%) in a phase II prime-boost vaccine trial in 27 patients with vulval intraepithelial neoplasia grade 3, and in 2 patients with vaginal intraepithelial neoplasia grade 3 [88].

The antigens of HPV viral vector therapeutic vaccine are mainly the E6 and E7 proteins, independent of or in the form of fusion proteins. Certain vaccines incorporate the E6 and E7 proteins of HPV18 to broaden the potential beneficiary population of the vaccine. It is worth mentioning that researchers have gradually begun to apply bioinformatic methods to design and construct target proteins to achieve immunogenic coverage of more HPV types: researchers designed the synthetic gene '5GHPV3' by selecting conserved regions from each of the six early proteins and generating consensus sequences to represent five hrHPV genotypes and inserted the '5GHPV3' separately ChAdOx1 and modified vaccinia MVA vectors to conduct ChAdOx1-HPV and MVA-HPV [89]; PRGN-2012 is built on a gorilla adenovector platform with a fusion of regions from HPV proteins selected by bioinformatic approaches and protein engineering to elicit immune responses directed against HPV-infected cells [15].

A rigorous clinical trial evaluating the safety and immunogenicity of Ad26—and MVA vector vaccine components was conducted among women with cervical infections caused by HPV16 or HPV18 (NCT03610581). It is noteworthy that PRGN-2012 is indicated for the treatment of recurrent respiratory papillomatosis, papillomavirus infections, and Papillomaviridae, which stimulate immune responses against the low-risk HPV6/11 types [15]. The HPV therapeutic vaccines are universally used to treat cancers and precancerous lesions. During tumor formation, an immunosuppressive microenvironment is formed, with downregulation of MHC molecules, infiltration of Treg cells, and excessive expression of immune checkpoint proteins such as PD-L1 [90]. Therapeutic vaccines are capable of elevating the levels of systemic cytotoxic CD8 + T cells and facilitating an increase in CD8 + cell counts within tumor tissue. On this basis, studies have confirmed that a tumor vaccine combined with immune checkpoint blockade (ICB) can greatly improve tumor response rates and enhance anti-tumor immune responses [91, 92]. From clinical trials of viral vector HPV treatment vaccines, if HPV-related tumors are selected as an indication, researchers will choose PD1/PD-L1 inhibitors as co-use drugs, such as Atezolizumab, Pembrolizumab, and Avelumab. As reported in European Society for Medical Oncology (ESMO) meetings in 2020, after therapeutic vaccination with TG4001 co-administered with Avelumab in 34 patients with various recurrent/metastatic HPV-positive cancers, one patient demonstrated complete response (CR), and seven patients achieved partial response per RECIST versus 1.1 [93]. Thus, combinations of tumor-therapeutic vaccines and immune checkpoint inhibitors represent an important direction for future treatments.

Viral vectors can also produce potent immune responses, including anti-viral cellular immunity and neutralizing antibodies [94–96]. Therefore, some researchers choose a heterologous vector booster vaccination to stimulate a stronger anti-HPV immune response, similar to prime-boost vaccines ChAdOx1-HPV and MVA-HPV, and prime-boost vaccines Ad26.HPV16 and MVA.HPV16/18 [89].

Conclusions

This paper summarizes progress in the development of therapeutic HPV vaccines using recombinant viral vectors, including viral vectors, antigen selection, efficacy assessment, and clinical trials. Currently, HPV-related tumor vaccines primarily achieve their efficacy by inducing immune responses and suppressing tumor growth. Several viral vector-based therapeutic HPV vaccines have entered clinical trials, exhibiting satisfactory safety profiles and tolerability. Additionally, they have demonstrated encouraging immunogenicity and tumor suppressive effects in terms of their therapeutic efficacy. HPV vaccines based on viral vectors hold promising prospects for future development.

In future studies, therapeutic viral vector HPV vaccines will be developed in the following directions: 1. Investigate safer and more effective viral vectors that exhibit reduced virulence in the population while maintaining their ability to infect a greater number of APC cells, thereby eliciting

Table 2 Progress in the clinical trials of HPV therapeutic vaccines utilizing live virus vectors

Vaccines	Types	Design	ClinicalTrials.gov Identifier	Phase	Recruitment Status	Conditions	Combination	Number Enrolled	Results	References
Ad-E6E7	HPV16/18	Ad5 (ΔE1/E3) HPV16/18 E6/E7 fusion protein	NCT03618953	phase I	Terminated[a]	HPV associated cancers	MG1-E6E7 and Atezolizumab	8	Not posted	[17]
TA-HPV	HPV16/18	Vaccinia virus Wyeth HPV16/18 + E6/7	NCT00002916	Phase II	Completed	Stage Ib or IIa cervical carcinoma, squamous or adenocarcinoma suitable for surgical excision	Surgery	44	28 patients were included in the initial stage, and 4 patients developed HPV-specific CTLs and 8 patients developed HPV-specific serological responses. The ultimate results haven't been posted	[16]

Table 2 (continued)

Vaccines	Types	Design	ClinicalTrials.gov Identifier	Phase	Recruitment Status	Conditions	Combination	Number Enrolled	Results	References
TG 4001	HPV 16	MVA [Ankara], IL-2, HPV16 E6/E7	NCT03260023	Phase Ib/II	Recruiting	HPV-Related Carcinoma HPV-Related Cervical Carcinoma HPV-Related Anal Squamous Cell Carcinoma HPV-Related Penile Squamous Cell Carcinoma HPV-Related Vulvar Squamous Cell Carcinoma	Avelumab	150	ORR was 22% (8/36) and 32% (8/25) in all and patients without liver metastases, respectively. PFS and OS were 2.8 months (95% CI: 1.4–5.6) and 11.0 months (95% CI:7.5–16.7) in the total population and 5.6 months (95% CI:1.6–9.6) and 13.3 months (95% CI:8.7–32.7) in patients without liver metastases	[18]
Vvax-001	HPV 16	Semliki Forest virus (rSFV) HPV16 E6/E7 fusion protein	NCT03141463	Phase I	completed	CIN 2/3 Cervical Cancer	-	12	Not posted	[19]
Vvax-001	HPV 16	Semliki Forest virus (rSFV) HPV16 E6/E7 fusion protein	NCT06015854	Phase II	Recruiting	CIN3 Cervical Intraepithelial Neoplasia Cervical Intraepithelial Neoplasia Grade 3 HPV 16 Infection	-	18	Not posted	

Table 2 (continued)

Vaccines	Types	Design	ClinicalTrials.gov Identifier	Phase	Recruitment Status	Conditions	Combination	Number Enrolled	Results	References
PRGN-2009	HPV16/18	gorilla adenovirus, HPV16/18 E6/E7 proteins	NCT04432597	Phase I/II[b]	-[b]Active, not recruiting	HPV Positive CancerVulvar, Vaginal, Penile, Rectal CancerAnal CancerOropharyngeal CancerCervical Cancer	Alone or in Combination With Anti-PDL1/TGF-Beta Trap (M7824)	39	There were no dose limiting toxicities.One of ten patients evaluable for response showed complete response and two showed partial response Post vaccination 14/16 (88%) patients developed T cell r esponses to HPV 16 and/or HPV 18	[20]
ChAdOx1-HPV[c]	HPV16/18/31/52/58	ChAd HPV16/18/31/52/58 E1/E2/E4/E6/E7	NCT04607850	Phase 1b/2	Completed	Low-grade HPV-related Cervical Lesion	prime-boost vaccines ChAdOx1-HPV and MVA-HPV	99	Not posted	[21]
MVA-HPV[c]	HPV16/18/31/52/58	MVA HPV16/18/31/52/58 E1/E2/E4/E6/E7								

Table 2 (continued)

Vaccines	Types	Design	ClinicalTrials.gov Identifier	Phase	Recruitment Status	Conditions	Combination	Number Enrolled	Results	References
HB-201	HPV 16	arenavirus LCMV + HPV16 E6/E7	NCT04180215	Phase I/II	Recruiting	HPV-Related Squamous Cell Carcinoma	HB 201;HB 202 + HB 201;HB 201 i + standard of care regimen including pembrolizumab; HB 202 / HB 201 + standard of care regimen including pembrolizumab; HB 202 / HB 201 + pembrolizumab	200	Not posted	[22]
HB-202	HPV 16	arenavirus HPV16 E6/E7								
Ad26.HPV16	HPV 16	Ad26 ΔE1/E3 + HPV 16 E6/E7 fusion protein	NCT03610581	Phase I	Terminated[d]	Human Papillomavirus Infections	Ad26.HPV16 MVA.HPV16/18 Ad26.HPV 18 + MVA.HPV16/18 Ad26.HPV16 Ad26.HPV18 + MVA HPV16/18	9	4 participants received Ad26.HPV16 (Regimen 1a) or Ad26.HPV18 (Regimen 1b) on Day 1 followed by MVA.HPV16/18 on Day 57. Patients	[23]
MVA.HPV16/18	HPV 16/18	MVA HPV 16 or 18[e]								

Table 2 (continued)

Vaccines	Types	Design	ClinicalTrials.gov Identifier	Phase	Recruitment Status	Conditions	Combination	Number Enrolled	Results	References
PRGN-2012	HPV6/11	GC46 gorilla adenovector + a fusion of regions from HPV Proteins against HPV6/11	Proteins against HPV6/11	Phase I/II	Active, not recruiting	Recurrent Respiratory Papillomatosis Papillomavirus Infections Papillomaviridae	-	38	As of June 20, 2023, it resulted in 50% of patients (6 out of 12) in CR, reduction of surgeries in 83% (10 out of 12) patients, and robust de novo HPV-specific T-cell immune response in RRP patients	[15]

[a]Virus potency titer of drug product as determined by an improved potency assay was lower than originally determined by the assay described in the IND

[b]Precigen Receives FDA Clearance of IND to Initiate Phase 2 Study of PRGN-2009 Off-the-Shelf AdenoVerse Immunotherapy in Combination with Pembrolizumab to Treat Patients with Recurrent or Metastatic Cervical Cancer

[c]They are aslo called VTP-200

[d]Low enrolment and increasing COVID restrictions, following an earlier enrolment pause in April made it clear that completion of the study would not be feasible

[e]No details were retrieved

a more potent cellular immune response. 2. Antigens not limited to E6 or E7. Leveraging bioinformatics, we aim to devise an enhanced "super antigen" that exhibits broadened coverage against multiple HPV types and is compatible with a wider range of HLA typing individuals. And attention must be paid to certain matters during the development process:1. The selection of suitable platforms for the preclinical assessment of vaccine efficacy in vitro is crucial. 2. As more clinical trial data becomes available, the therapeutic strategies for HPV vaccines will be gradually consummate.

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Declarations

Conflict of interest The authors declare no competing interests.

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