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Advances in HPV Vaccine Development: Toward Combined Prevention and Treatment Strategies

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Abstract: Human papillomavirus (HPV) causes cervical and other cancers, but first-generation L1 vaccines are underused and cannot treat existing infections. Research shows that the activities of p53 and pRb can be inhibited by proteins E6 and E7, promoting cancer development. These insights have led to new vaccine platforms that aim to both prevent and treat HPV infection. Clinical trials are testing L2-based, DNA, peptide, and mRNA vaccines. However, no single vaccine yet offers broad protection, treatment effectiveness, low cost, and stability in field settings. This review describes HPV biology, explains how E6 and E7 drive cancer, and assesses the strengths and weaknesses of current L1 vaccines. It also reviews next-generation approaches such as L2 vaccines with broader coverage, DNA and peptide vaccines that reduce lesions, and mRNA vaccines showing tumour clearance in early studies. Examples include VGX-3100, imiquimod-based regimens, and first-in-human mRNA vaccines. The review outlines a combined prevention-and-treatment strategy for HPV-related diseases. Future work should focus on large global trials, combinations with checkpoint inhibitors, and affordable, heat-stable vaccines for use in resource-limited areas. Success in these areas could greatly reduce world impact of HPV-related diseases.

Keywords: Human Papillomavirus (HPV), Therapeutic Vaccine, mRNA Platforms.

1. Introduction

Human papillomavirus (HPV) accounts for around 5% of cancers in the world, over 90% of cervical cancer cases are attributed to persistent infections with high-risk types of HPV. To prevent HPV infection, regular screening is essential, however, vaccination remains the most effective preventive strategy against infectious diseases. Although the licensed bivalent, quadrivalent and nonavalent L1-VLP vaccines have dramatically reduced HPV infection rates in regions with high uptake, only 27 % of the world's target population received a first dose in 2023, and these vaccines cannot eliminate pre-existing lesions. Bridging the gap between prevention and treatment is therefore an urgent public-health and research priority.

Molecular studies have proved that the E6/E7 cancer-related proteins are the main engines of HPV-associated tumor initiation and progression, they disable the p53 and pRb tumor-suppressor safeguards and active multiple cancer-linked pathways, giving HPV-infected cells limitless growth, invasive power, immune evasion, and metabolic advantages [1]. The latest research has found that E6/E7 also affects histone-modifying enzymes (such as p300), epigenetic states, DNA damage

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responses, and cell survival pathways, thereby promoting malignant transformation [2]. Clinically, E6/E7 mRNA expression associated with progression from Cervical intraepithelial neoplasia (CIN)to invasive carcinoma, underscoring their pathogenic importanc.

Current research demonstrated that the licensed L1-VLP vaccines have near-complete efficacy against HPV-16/18 and moderate cross-protection (74-93%) in adolescents aged from 9 to 14 [3]. Nevertheless, these vaccines remain efficacy to specific genotype and have no therapeutic effect on established infections. To overcome these limits, research is now exploring next-generation vaccines: L2-based broad-spectrum platforms, therapeutic vaccines targeting E6/E7, and mRNA or nanoparticle-based formulations. By optimizing the mRNA construct and delivering it via lipid nanoparticles (LNPs), recent research has successfully developed an L2-mRNA vaccine that targets HPV-6/11/16/18 while also providing cross-protection against several high-risk types (such as 31 and 52) [3]. A head-to-head mouse study showed that a single 1 μg dose of self-amplifying or nucleoside-modified E7-gD mRNA-LNP eradicated HPV-driven tumours and generated durable memory $CD8^+$ T-cell immunity, markedly outperforming both the VGX-3100 DNA vaccine and a recombinant-protein comparator [4]. These results signal a shift from purely preventive immunisation toward “preventive-plus-therapeutic” HPV vaccination strategies.

This article aims to integrate the recent molecular research results on the mechanism by which E6/E7 proteins cause cancer, and to assess how these findings can support the development of new-generation HPV vaccines. By evaluating L2, E6/E7 therapeutic, and mRNA/nanoparticle-based strategies, this paper explores new pathways for achieving broad protection and therapeutic potential, providing strategic references for improving the prevention and control of global HPV-related cancer.

2. Mechanism of HPV infection and pathogenesis

2.1. HPV structure, genome, and classification

HPV, belongs to the Papillomaviridae family, is a small, unenveloped virus, the icosahedral capsid structure is 50-55 nm. Its genome is a circular, ds DNA molecule of around 8,000 base pairs long, encoding early and late genes, along with a long control region (LCR) which is essential for replication and transcriptional regulation [5]. The early genes primarily regulate viral replication and pathogenesis, whereas late genes encode capsid proteins essential for viral assembly and infectivity. HPV is classified into 2 types based on their oncogenic potential. High-risk (HR) HPV types such as HPV-16, HPV-18, HPV-31, and HPV-52 are strongly associated with malignant transformation and cervical cancer, while low-risk (LR) HPV types, including HPV-6 and HPV-11, typically cause benign lesions like genital warts [6].

2.2. Molecular mechanisms of HPV infection

The molecular mechanism of HPV infection initiates when viral particles infect basal cells of the epithelium through abrasions. The L1 capsid protein mediates initial binding to the host cells through its interaction with heparan sulfate proteoglycans (HSPGs) on the cell surface. After that, conformational changes allow L2 to facilitate viral internalization, the viral genome is transferred into the host cell nucleus, where initial replication occurs [7]. The life cycle of the virus relates to the differentiation process of host cell. Early viral proteins E1 and E2 facilitate viral DNA replication and transcription control, whereas E4 contribute to the disruption of cytoskeletal networks, thereby enhancing viral particle release from superficial epithelial layers. Concurrently,

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E5 modulates cellular signalling pathways to evade immune evasion and promote cell proliferation [8].

2.3. Oncogenic mechanisms of HPV

The carcinogenic potential of human papillomavirus is mainly caused by persistent infection and the continuous expression of viral oncogenes E6 and E7. The E6 protein interacts with E6-AP, attributing to the ubiquitination-mediated degradation of the tumour suppressor protein p53, which compromises cell-cycle arrest and apoptosis, thereby facilitating the accumulation of genetic damage and unchecked cell proliferation [9]. Meanwhile, the E7 protein targets the retinoblastoma protein (pRb), thus disrupting its regulation of E2F (E2 Factor) transcription factors and leading to uncontrolled G1-to-S phase transition, increased genomic instability, and cellular transformation [10]. Recent studies have identified additional molecular mechanisms driven by E6 and E7, including interactions with histone-modifying enzymes such as p300, alterations in epigenetic regulation, and disruption of DNA damage repair pathways, all of which further contribute to malignant progression [11]. Clinically, persistent expression of E6/E7 mRNA correlates strongly with disease progress from cervical intraepithelial neoplasia (CIN) to invasive carcinoma, underscoring their central role in HPV-induced carcinogenesis and highlighting their value as therapeutic target [12].

3. Current situation and limitations of existing HPV vaccines

3.1. vFirst and second-generation HPV vaccines

Currently, approved HPV vaccines include the first-generation bivalent vaccine (Cervarix), quadrivalent vaccine (Gardasil), and the second-generation nine-valent vaccine (Gardasil 9). These vaccines use virus-like particles (VLPs) made from the L1 protein. They can trigger strong immune responses and produce antibodies to protect against HPV infections. Clinical studies show these vaccines have very high effectiveness (over 90%) against the HPV types they target. They greatly reduce cases of cervical pre-cancer and genital warts around the world. The nine-valent vaccine covers more HPV types, such as HPV-31, 33, 45, 52, and 58. This provides broader protection compared to the bivalent and quadrivalent vaccines [13].

However, these vaccines have some limits. They offer only limited protection against HPV types that are not included in the vaccines. It is still unclear how long the vaccines' protection lasts. People may need booster shots in the future. Also, current vaccines cannot treat existing HPV infections or lesions. They can only prevent infections.

3.2. Challenges of HPV vaccination

There are many challenges in promoting HPV vaccines around the world. By 2023, only around 27% of the target population globally had received at least one dose of the vaccine. Vaccine hesitancy, misinformation, high costs, poor healthcare systems, and cultural issues are major obstacles. These problems are more serious in low- and middle-income countries. According to the research from Gavi, the Vaccine Alliance, in 2022, the market price of the HPV vaccine ranges from approximately $30 to $100 per dose. However, the annual per capita health expenditure in many low-income countries is only several dozen dollars, which is clearly inadequate to cover such high costs. Although international organizations such as Gavi have managed to reduce the vaccine price to below $5 per dose through financial subsidies, numerous middle-income countries that do not

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qualify for Gavi's support continue to face substantial economic challenges. These financial constraints have hindered the effective implementation of vaccination programs and limited progress in expanding vaccination coverage. Besides, the issue of vaccine hesitancy is also quite serious, especially in low-income and middle-income countries (LMICs). A global survey indicates that in Africa and South Asia, the proportion of vaccine hesitancy can reach 30% to 40%, significantly higher than the 10% to 20% in high-income countries [14]. The main reasons for this include public concerns about the safety and efficacy of vaccines, lack of trust in the medical system and the government, insufficient knowledge of vaccines, and the influence of local traditional beliefs and religious practices.

Another issue is the vaccine's need for cold storage and multiple doses. This makes it hard for people in poor areas to get vaccinated. From a scientific point of view, current vaccines protect only against specific HPV types. They are not effective against other HPV types that may be common in different parts of the world. Another important issue is that these vaccines have no therapeutic effect. They cannot help clear existing HPV infections or treat related diseases.

4. Development progress of next-generation HPV vaccines

4.1. Novel vaccine development strategies

Scientists are now working on new types of HPV vaccines to solve the problems of existing vaccines. One approach is using the L2 protein instead of L1 for making vaccines. L2 protein can provide protection against more types of HPV. Researchers have developed an mRNA vaccine using L2 protein. This vaccine targets HPV types 6, 11, 16, and 18, and can also protect against some other high-risk type [3]. Another type of new vaccine focuses on therapeutic use. This type targets HPV proteins E6 and E7, which cause cancer. Researchers are using methods like DNA, peptides, or mRNA to help the immune system fight existing HPV infections and cancer. mRNA vaccines have become popular due to their effectiveness. These vaccines use LNPs to deliver mRNA into the body. Recent animal studies show that even a single dose of mRNA vaccine targeting E7 protein can eliminate HPV-related tumours in mice. These vaccines also created long-lasting immune responses [4].

4.2. Clinical studies and prospects of new HPV vaccines

Several new vaccines are now being tested in clinical trials. For example, therapeutic vaccines targeting HPV E6 and E7 are being tested on patients who already have HPV-related cancers or pre-cancerous conditions. In a phase II clinical trial combining imiquimod treatment with an HPV therapeutic vaccine, nearly 60% of women with high-grade, long-standing vulvar intraepithelial neoplasia (VIN), who had previously undergone multiple treatments, achieved histological clearance at 52 weeks. Similarly, in a phase IIb randomized, placebo-controlled trial, the DNA vaccine VGX 3100—targeting HPV 16/18 E6 and E7—achieved histologic regression in approximately 50% of women with CIN2/3 and induced strong HPV-specific T-cell responses, with good safety and tolerability. These findings suggest that therapeutic HPV vaccines show promising results in reducing disease burden and enhancing immune responses.

mRNA vaccines are also moving quickly toward clinical trials. Their ability to protect against multiple HPV types makes them highly promising. For instance, the mRNA vaccine candidate LY01620, developed by Luye Pharma, has received regulatory approval to enter a Phase I clinical trial targeting HPV 16–related high-grade squamous intraepithelial lesions (HSIL). This vaccine

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uses an LNP-formulated mRNA encoding E6/E7 proteins and represents the first therapeutic mRNA HPV vaccine to reach human trials in China. Similarly, RinuaGene's mRNA vaccine is currently being tested in a Phase I/II trial (NCT06273553) involving women with HPV 16/18–positive cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3). The study evaluates different dosing regimens and monitors histological regression, viral clearance, and T-cell–mediated immune responses. These early clinical trials indicate that mRNA-based HPV vaccines are safe, immunogenic, and potentially effective, offering great promise for future widespread use

mRNA vaccines are also moving quickly toward clinical trials. For example, a recent preclinical study developed an mRNA-based therapeutic vaccine, mHTV-03E2, formulated with lipid nanoparticles and targeting E2, E6, and E7 antigens of both HPV16 and HPV18. This vaccine induced strong antigen-specific $CD8^+$ T cell responses in TC-1 tumor-bearing mice, leading to significant tumor regression, prolonged survival, and enhanced memory T cell immunity lasting up to four months. Moreover, mHTV-03E2 showed synergistic effects when combined with immune checkpoint inhibitors, suggesting potential for combination therapy. Researchers believe these vaccines might soon be ready for widespread use.

5. Challenges and future perspectives

Developing new HPV vaccines still faces several problems. First, it is difficult to produce a vaccine that protects against all HPV types. Each type of HPV may need a different approach, making vaccine design complicated. Second, there is the challenge of proving that these vaccines work in humans through clinical trials. This step requires lots of resources and takes a long time. Another big challenge is ensuring the new vaccines are affordable and easy to distribute. Currently, advanced vaccines like mRNA types require special storage conditions. This makes it difficult to provide these vaccines in poor or remote areas. Scientists need to find ways to make vaccines cheaper, easier to store, and distribute. Overall, despite these challenges, research continues to advance quickly. New HPV vaccines hold the promise of significantly reducing HPV-related diseases worldwide.

6. Conclusion

This review examines the evolution of HPV vaccines over time. It begins by describing the first-generation L1 VLP vaccines, which provide protection against a limited number of common HPV types. The review then explores emerging strategies aimed at both treating established infections and offering broader coverage across multiple HPV genotypes. Central to these developments are the viral oncoproteins E6 and E7, which inactivate the tumour-suppressor proteins p53 and pRb, thereby disrupting cell cycle regulation and promoting oncogenesis. Additionally, recent experimental evidence demonstrates that E6 and E7 also interfere with cellular signalling pathways and DNA repair mechanisms.

Next-generation vaccine approaches offer promising prospects for improved HPV control. L2-based vaccines demonstrate potential for cross-protective immunity against multiple HPV types. DNA, peptide, and mRNA vaccines encoding fragments of E6 and E7 have been shown to elicit robust cytotoxic T-cell responses. Preliminary clinical and preclinical studies indicate reductions in precancerous lesions and tumour regression in both human subjects and murine models. These findings suggest the possibility of developing vaccines capable of simultaneously preventing infection and treating HPV-associated diseases.

However, several limitations remain. Most available data derive from small-scale or animal-based studies, and long-term efficacy, safety, and scalability across diverse populations have yet to

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be fully established. Manufacturing and distribution challenges further limit accessibility, particularly in low-resource settings.

Future research should prioritize large-scale, multi-centre clinical trials to validate efficacy across broader populations. Investigations into combination therapies involving vaccines and immune checkpoint inhibitors should also be expanded. Vaccine developers must focus on creating thermostable formulations that eliminate dependence on cold-chain storage. Concurrently, public health initiatives must address cost barriers and vaccine hesitancy. If scientific innovation is matched by policy support, next-generation HPV vaccines may effectively bridge the gap between prevention and therapeutic intervention in HPV-related cancers.

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