Current Status of Human Papillomavirus Vaccines

Barbara Ma, Richard Roden, T.-C. Wu

Cervical cancer is the second leading cause of cancer deaths in women worldwide, with ~500,000 diagnoses and 274,000 deaths annually. It remains a significant source of morbidity and mortality despite effective screening tools and treatments for its precursor: high-grade cervical intraepithelial neoplasia (CIN). Increased understanding of cervical pathogenesis has led to the identification of human papillomavirus (HPV) as the etiological agent for cervical cancer, and the development of preventive and therapeutic vaccines that target HPV antigens for the control of cervical cancer. Here, we discuss the current status of HPV vaccines.

Currently Approved Prophylactic HPV Vaccines

The commercialization of two prophylactic HPV vaccines, Gardasil (Merck, Whitehouse Station, NJ, USA) and Cervarix (GlaxoSmithKline, Brentford, Middlesex, UK), represents a milestone for the prevention of cervical cancer. The vaccines target the HPV L1 major capsid protein, which can assemble to form virus like particles (VLPs) that resemble native virions morphologically, to generate robust antibody responses and prevent HPV infection. Gardasil contains VLPs for HPV-16 and HPV-18, which are associated with cervical cancer and VLPs for HPV-6 and HPV-11, which are associated with benign genital warts. Cervarix contains only HPV-16 and HPV-18 VLPs. Although both vaccines contain classical aluminum salt adjuvants, Cervarix also contains monophosphoryl lipid A, a Toll-like receptor 4 agonist that primes innate immunity and can stimulate adaptive immunity for enhanced antibody titers. The United States Food and Drug Administration approved Gardasil in 2006 for women aged 9–26 years. In October 2009, it approved Cervarix for use in women aged 10–25 years, and approved Gardasil for use in men aged 9–26 years to prevent genital warts and the spread of cervical cancer. These recent events could have a further impact on cervical cancer rates.

Issues Faced by Current Preventive HPV Vaccines

Although current preventive HPV vaccines are promising for global prevention of cervical cancer, there are some remaining issues.
Cost
The high cost, the need for refrigeration and multiple doses of the commercial preventive HPV vaccines preclude their widespread implementation in developing countries, which have more than 80% of cervical cancer cases. Gardasil and Cervarix each require three doses that cost $100/dose. For low-income countries, the per dose cost would need to be less than $5 for vaccination to be affordable. Employment of basic structural units of the HPV capsid assembled from five L1 monomers, termed L1 capsomers, represents a potential alternative because they are more thermostable and cheaper to produce than VLPs. L1 capsomers produced in Escherichia coli and expression of L1 in recombinant Salmonella enterica serovars. Typhimurium have been shown to induce protective antibodies in preclinical models. Other options include needle-free administration routes to lower complexity and vaccination cost.

Duration of vaccine efficacy
Duration of HPV vaccine efficacy is crucial in deciding whether cervical cancer is merely postponed or truly prevented. Analyses have indicated that duration must last at least 15 years for cost-effective prevention of cervical cancer. Although Cervarix and Gardasil are highly efficacious in preventing HPV-16/18-associated lesions, the duration of efficacy beyond 6.4 years for Cervarix and 5 years for Gardasil is unknown. In a head-to-head trial, Cervarix was shown to have somewhat higher antibody titers for HPV-16 and HPV-18 than did Gardasil, but it is unclear if this will translate into a more durable response. It will be important to follow up on these vaccines to see if two doses are sufficient, or if additional booster shots are required.

Coverage of HPV types
Gardasil and Cervarix contain VLPs for HPV-16 and HPV-18, which account for up to 75% of cervical cancers, with more than 10 HPV types accounting for the remaining cases. Unfortunately, these vaccine elicited antibody responses are primarily type restricted to the genotypes covered. Although limited partial cross protection has been observed against homologous HPV genotypes, the duration of cross protection is unknown. L1 vaccines that contain VLPs for multiple HPV types might broaden protection. Merck is recruiting for phase III clinical trials of a nine-valent vaccine, V503. Another promising method involves the L2 minor capsid protein, which is highly conserved across HPV genotypes. Efforts have focused on boosting the immunogenicity of L2 by linking together short amino acid sequences of L2 from different oncogenic HPV types. Although multimeric L2 has shown robust antibody responses in preclinical models against multiple HPV types, it is not as immunogenic as VLPs. Upon successfully finding an appropriate adjuvant, this approach will be explored in clinical trials.

Therapeutic HPV Vaccines
The existing global burden of HPV associated lesions and cervical cancer emphasize the urgent need for therapeutic HPV vaccines. Current preventive vaccines exert no therapeutic effects and it would take many years of mass vaccination to reduce cervical cancer rates, because of the high prevalence of HPV infection and the slow rate of cervical carcinogenesis. In contrast to antibodies induced by preventive vaccines, therapeutic vaccines aim to generate cell-mediated immune responses using killer T cells that actively destroy HPV-infected cells. Hence, therapeutic vaccines can exert immediate effects on lowering HPV-related disease incidence.

Although definitive objectives have been achieved in developing preventive HPV vaccines, overall progress in therapeutic HPV vaccine development has been slower. Vaccination to control cervical cancer has been evaluated in several forms, such as live vector-, peptide/protein-, nucleic acid- and whole-cell-based therapeutic HPV vaccines that target HPV E6 and E7 oncoproteins. The promising preclinical data have led to the evaluation of several therapeutic vaccine candidates in early phase clinical trials.
Long overlapping peptides have stirred enthusiasm for therapeutic HPV E6/E7 peptide-based vaccines because they could limit the obstacle of major histocompatibility complex restriction by broadening the range of antigenic epitopes. A vaccine comprised of 13 overlapping peptides that represents HPV-16 E6 and E7, formulated in Montanide ISA 51 adjuvant, has been shown to be safe and well tolerated in earlier trials, and has most recently demonstrated great efficacy in a phase II trial, thus leading to complete clinical responses in nine of 19 patients with evaluable HPV-16-positive, high-grade, vulvar intraepithelial neoplasms.9

DNA vaccines that employ strategies to enhance vaccine potency have also stimulated great interest. Microencapsulation of DNA vaccines can prevent DNA degradation by nucleases, for efficient delivery. Amolimogene bepiplasmid (ZYC101A), a DNA vaccine comprised of plasmid DNA that encodes HPV 16/18 E6/E7 proteins encapsulated in poly (glycolide-lactide) biopolymer, has advanced to phase II/III clinical trials and is undergoing investigation in CIN 2/3 patients.10 Other vaccine potentiating approaches include intracellular targeting strategies that utilize the understanding of antigen processing/presentation pathways. One example is Sig/E7(detox)/Hsp70, a DNA vaccine that encodes a signal sequence for the endoplasmic reticulum that is linked to an attenuated form of HPV-16 E7 and fused to immunostimulatory Hsp70. A phase I clinical trial of Sig/E7(detox)/Hsp70 boosted with recombinant vaccinia virus that encodes HPV-16/18 E6/E7 fusion protein (TA-HPV), with or without imiquimod, is in progress in CIN 2/3 patients.11 Additionally, a phase I trial has recently begun to evaluate CRT/E7 (detox), a DNA vaccine that encodes modified HPV-16 E7 linked to calreticulin, delivered via a clinical grade gene gun, in patients with high-grade CIN (oral communication with Dr W Huh, November 2009).

**Future Outlook**

Although it is clear that HPV vaccines will not eliminate the need for effective cervical screening and treatment for many years to come, they can substantially reduce the burden that cervical cancer imposes on women and health services in the long run. Although significant challenges remain in achieving broad coverage of adolescents and reducing the cost of these vaccines, the implementation of two commercial preventive HPV vaccines has exciting prospects. Additionally, with continuing progress into the advanced stages of clinical trials and further exploration of combinatorial strategies, there is great promise for significant advances in the field of therapeutic HPV vaccine development.

**References**

11. NCI. Vaccine Therapy With or Without Imiquimod in Treating Patients With Grade 3 Cervical Intraepithelial Neoplasia. Available at: http://clinicaltrials.gov/ct2/show/NCT00788164