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Preventing Cancer and Other Diseases Caused by Human Papillomavirus Infection:

2017 Lasker-DeBakey Clinical Research Award

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Abstract

The 2017 Lasker-DeBakey Clinical Medical Research Award has been presented to Douglas Lowy and John Schiller for development of the virus-like particle technology that was used to create the human papillomavirus vaccine to prevent cervical cancer and other diseases.

The sexually transmitted nature of cervical cancer was recognized by Rigoni-Stern in the 19th century, and human papillomavirus (HPV) infection was known from the early 20th century to cause genital and nongenital warts. However, the medical importance of these viruses was not clearly established until the 1980s with the break-through discovery by zur Hausen[1] and colleagues that HPV type 16 (HPV-16) or HPV type 18 (HPV-18), which were distinct from the HPV types causing genital warts, was found in approximately 70% of cervical cancers, the third most common cancer among women worldwide.

Further studies from many basic virology and epidemiology groups led to the conclusion that HPV infection was the cause of different forms of cancer. The approximately 30% of cervical cancers that are not attributable to HPV-16 or HPV-18 are caused from infection by 1 of at least 10 other HPV types.[2] A subset of HPV types associated with cervical cancer, especially HPV-16, are also a cause of many cases of anal, vulvar, vaginal, penile, and oropharyngeal cancer, which are much more common among men and have increased more than 3-fold during a recent 25-year period. Screening for cervical cancer has reduced the incidence and mortality of this disease in the United States, and there are now fewer cases of cervical cancer than of other HPV-associated cancers. By contrast, cervical cancer accounts for approximately 90% of the HPV-associated cancers in the developing world, where the annual number of deaths from this cancer are projected to increase from 206 000 in 2015 to 317 000 in 2030.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Lowy reported holding a patent for virus-like particle L1 human papillomavirus (HPV) vaccine licensed to Merck, GlaxoSmithKline, and Indian Immunologicals Ltd. Dr Schiller reported being an inventor on patents owned by the US government with royalties paid by Merck and GlaxoSmithKline.

Developing a Virus-like Particle Vaccine

Starting with the prevention of smallpox, vaccination has been a cost-effective approach to reduce the risk of disease caused by infectious agents. It has proven easier to induce protective immunity against incident infection and disease than treat prevalent infection and disease. The cornerstone of most preventive vaccines is their induction of toxin- or infection-neutralizing antibodies. The 2 proteins that comprise the HPV virion shell (L1 and L2) each contain neutralization epitopes. The L1 protein contains the immunodominant epitopes, but those that induce infection-inhibiting antibodies are dependent on conformation, suggesting a virus-like particle (VLP) structure would be the most likely to display them. Because all HPV types contain oncogenes, a subunit vaccine lacking them would be needed in a preventive vaccine.

Given this background, Kirnbauer, Lowy, Schiller, and colleagues established the concept of expressing L1 alone via a recombinant baculovirus vector in insect cells, which led to the self-assembly of VLPs that induce high titers of neutralizing antibodies.[3]The VLP structure was necessary because denatured VLPs induced only nonneutralizing L1 antibodies. These initial observations were made with bovine papillomavirus type 1(BPV-1) because the investigators had infectious BPV-1 and had developed a quantitative in vitro BPV-1 infection–neutralization assay.

Earlier studies with HPV-16 by Zhou, Frazer, and colleagues reported that expression of L1 alone did not stimulate VLPs, whereas coexpression of L1 and L2 resulted in aberrant particles.[4] Indeed, when Kirnbauer, Lowy, and Schiller attempted to extend their results to HPV-16 L1, it self-assembled about 3 orders of magnitude less efficiently than with BPV-1. The researchers speculated the L1 being used, which was from the zur Hausen reference strain, was a mutant because it had been isolated from cervical cancer. Therefore, they tested HPV-16 L1 isolates from nonmalignant lesions, which assembled as efficiently as BPV-1.[3] Sequence analysis determined that 1 of the wild-type strains differed from the mutant reference strain by a single amino acid. When Roden, Lowy, and Schiller developed a neutralization assay for HPV-16, they found wild-type L1 induced antibodies with high-neutralizing activity, whereas L1 from the reference strain did not.[2]

Preclinical Vaccine Testing

At the time of these studies in the 1990s, the species-specific nature of the types of HPV meant that in vivo preclinical vaccine studies needed to be conducted with animal papillomavirus systems. Vaccine studies of canine papillomavirus by Schlegel, Suzich, Ghim, and colleagues and rabbit papillomavirus by Breitburd, Lowy, Schiller and colleagues independently demonstrated that VLPs induced strong protection against experimental challenge by the homologous animal papillomavirus and confirmed neutralizing antibodies could mediate the protection.[3] In vivo testing of BPV type 4 (BPV-4) VLPs in cows by Campo, Lowy, and Schiller confirmed the prophylactic efficacy of the vaccine, and established the vaccine was not therapeutic because it did not induce regression of established BPV-4 lesions. An in vitro assay with VLPs from various HPV types conducted by Roden, Lowy, and Schiller suggested that immunity to HPV-16 or HPV-18 would not

confer protection against the heterologous type, although there could be some cross-protection against more closely related types, implying protection would be restricted by HPV type and a vaccine with VLPs from several HPV types would be needed.[2]

HPV Vaccination in Humans

In early-phase clinical trials conducted in young women and men, Harro, Lowy, and Schiller showed a monovalent HPV-16 L1 VLP vaccine was well tolerated and highly immunogenic.[2] Significant efficacy results were then found In a placebo-controlled trial of an HPV-16 L1 VLP vaccine; none of the 768 women who received the experimental vaccine developed new HPV-16 infection, whereas 41 of the 765 women in the placebo group did.[5] Although the vast majority of vaccines prevent disease rather than infection, sterilizing immunity accounted for most of the HPV vaccine–induced protection. International trials of a quadrivalent VLP vaccine (HPV type 6, HPV type 11 [HPV-6 and HPV-11 account for approximately 90% of genital warts], HPV-16, and HPV-18) and a bivalent VLP vaccine (HPV-16 and HPV-18) conferred 95% efficacy in young women against incident cervical disease for each HPV type targeted by the respective vaccine, leading to approval from the US Food and Drug Administration (FDA) in 2006 and 2009, respectively, for the vaccines made by Merck and GlaxoSmithKline.[2] The vaccines were the first to successfully prevent development of local sexually transmitted disease.

Efficacy trials of the quadrivalent vaccine in males, which used anal dysplasia as the clinical end point, led to FDA approval of this vaccine for males in 2009. A second-generation 9-valent vaccine was developed, adding VLPs of the 5 HPV types found most commonly in cervical cancer after HPV-16 and HPV-18 because the quadrivalent vaccine induced limited cross-protection against HPV types not specifically targeted by the vaccine. This vaccine was approved by the FDA for males and females in 2014. In Australia, where only women were vaccinated between 2007 and 2013, high uptake of the quadrivalent vaccine after its licensure resulted in high effectiveness in women, and also strong herd immunity, leading to an approximately 4-fold reduction among young Australian-born males in the prevalence of the 4 HPV types targeted by the vaccine and the incidence of genital warts.[6]

Reducing Vaccine Doses and Increasing Uptake

Based on prior experience with other subunit vaccines, the HPV vaccines were initially administered in 3 parenteral doses over a 6-month period, which induced high antibody titers in the vast majority of vaccine recipients. Studies conducted after each vaccine was approved by the FDA indicated that when young adolescents were given 2 vaccine doses separated by at least 6 months, the resulting HPV antibody titers were at least as high as those in the women receiving 3 doses in the respective efficacy trials, which led to regulatory approval for 2 doses in young adolescents.[7]

Vaccine studies have raised the possibility that even a single dose may be able to confer long-term protection. In post hoc analyses of bivalent and quadrivalent vaccine clinical trials, high efficacy was observed when a woman received 1 dose, 2 doses, or the full 3-dose schedule (M. Safaeian, PhD, MPH, unpublished data, August 2017). Even more surprising,

the HPV-16 and HPV-18 serum antibody titers among the women who received only 1 dose of the bivalent vaccine reached a plateau level within 1 year after vaccination that was only 4 times lower than those who received all 3 doses, and these levels have remained stable for 7 years after vaccination (M. Safaeian, PhD, MPH, unpublished data, August 2017). There is no precedent for a single dose of a subunit vaccine inducing such a sustained response, which usually occurs only with live attenuated vaccines. The particulate and repetitive structure of the VLPs likely contribute to the consistency and durability of the antibody response.[2]

A rigorous clinical trial jointly sponsored by the National Cancer Institute and the Bill and Melinda Gates Foundation has begun that will test the efficacy of a single dose of the bivalent and 9-valent vaccines in young adolescent girls (NCT03180034). If the trial demonstrates a single dose of at least 1 of the vaccines can induce long-term protection, it has the potential to change worldwide recommendations. A single vaccine dose would be both less expensive and logistically easier to administer, which could greatly increase uptake, especially in low-resource settings where HPV-associated cancer poses the greatest public health problem and HPV vaccine uptake has been limited. A successful outcome from a single dose will also imply that serious consideration should be given to a VLP or an analogous repetitive structure for the development of future vaccines.

Conclusions

Research by many groups contributed to understanding the role of HPV in cancer and developing the HPV vaccine. Two pharmaceutical companies (Merck and GlaxoSmithKline) took a chance on the vaccine despite the poor prior track record for vaccines against sexually transmitted infections in which disease develops at the portal of infection. Trial participants played an indispensable role in the clinical trials that have been completed and will continue to be critical to the success of ongoing and future trials. The long-term goal of eliminating HPV-associated cancer as a public health problem has now become feasible. However, enabling worldwide uptake of the vaccine is required to realize that goal.

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