EDITORIAL

Human papillomavirus (HPV) vaccines: prospects for eradicating cervical cancer

Introduction
One of the most important developments of the past 25 years in cancer biology has been the evidence that infection with human papillomaviruses (HPVs) in the lower genital tract is the cause of virtually all cases of cervical carcinoma in women and a smaller, less defined fraction of vulvar, vaginal, anal and penile cancers. HPVs are members of a large family of viruses that infect squamous epithelial surfaces: the 35 HPV types that infect the genital tract fall into two discrete groups:

- Low-risk, non-oncogenic types 6 and 11 and their relatives that cause anogenital warts and are rarely detected in malignant disease.
- High-risk, oncogenic HPVs (hrHPV) types 16, 18, 31, 33, 35, 45, 52, 56 plus about eight other minor types. These can be detected in almost 100% of cervical cancer biopsies and more than 90% of the high-grade, cervical intra-epithelial neoplasia (CIN2/3) precursor lesions.

The causal link between HPV infection and cervical cancer has now been established beyond reasonable doubt. HPV 16 is the most frequently detected HPV in cervical cancers (about 50–60%) with HPV 18 (10–12%) being the second most common.

The implication of this is that intervention against this viral infection should prevent the vast majority of cervical cancers cases worldwide. Vaccines are the traditional cost-effective means to prevent microbial- and viral-induced diseases: HPV should be no exception and, indeed, substantial progress has been made in the past decade in the development of vaccines to prevent and/or treat these infections. Prophylactic HPV vaccines are in large Phase III trials, and several Phase II trials of therapeutic vaccines for the treatment of established HPV-induced intra-epithelial disease are either complete or in progress.

Prophylactic vaccines
The rationale for prophylactic HPV vaccines is that they induce the production of neutralising antibody to the virus and thus prevent infection on subsequent exposure. In low-risk HPV infections and natural infections in animals there are serum responses to virus coat proteins in individuals who are or who have been infected; in animal models such individuals are protected against subsequent viral challenge. In these cases, neutralising antibody is generated against determinants on the L1 protein (the major coat or capsid protein) exposed on the outer surface of the intact virus. A vaccine generating such responses must therefore contain L1 protein in the correctly folded tertiary or ‘native’ form. This is technically very difficult to achieve, but eventually it was shown that the L1 protein, when expressed by vectors such as recombinant baculovirus or yeast, self-assembles into virus-like particles (VLPs). The L1 VLP is a conformationally correct, empty capsid (i.e. it contains no DNA) that appears morphologically identical to, and contains the major neutralising epitopes of, the native virion. These VLPs are obvious vaccine candidates, and in Phase I studies in volunteers L1 VLPs were shown to be immunogenic, generating high titres of anti-L1 neutralising immunoglobulin G (IgG).

Two L1 VLP vaccines are now in Phase III trials: a bivalent HPV 16/18 VLP vaccine developed by GlaxoSmithKline (GSK) and a quadrivalent HPV 16/18/6/11 vaccine from Merck Vaccines. The preliminary efficacy data from Phase II proof-of-principle trials for VLP vaccines are immensely encouraging. A double-blind, placebo-controlled efficacy study of a yeast-derived HPV 16 L1 VLP vaccine developed by Merck was published in 2002. All vaccinees in the according-to-protocol group were protected from persistent HPV 16 infection, whereas in the placebo group 41 individuals acquired HPV 16 DNA, nine of whom also had HPV-related CIN. Equally encouraging data were reported for the GSK vaccine (a baculovirus-derived HPV 16/18 L1 VLP) at the 21st International Papillomavirus Workshop in Mexico City in March 2004. In a double-blind, placebo-controlled efficacy study, in the according-to-protocol group 100% of vaccinees were protected against persistent HPV 16 or 18 infection. Importantly, in the intention-to-treat group in this study, 94% of vaccinees were protected despite an incomplete vaccination regime. The results from the various trials strongly indicate that vaccination of previously uninfected women using HPV 16 or 18 L1 VLPs is safe and protective, preventing HPV 16 or 18 infection (as measured by acquisition of HPV 16 or 18 DNA) and the development of low-grade intra-epithelial lesions.

However, there are some important issues that must be considered. A key question concerns the duration of the protection induced by these vaccines. Will we need frequent booster immunisations? Preliminary data from several Phase II trials indicate that antibody levels fall from the peak levels achieved after immunisation to a low but measurable level that persists for at least 36 months post-vaccination. This is encouraging because it mirrors the situation in animal models where protection is long lasting, despite low levels of circulating antibody. However, the data from the trials cover a relatively short time span and, in reality, we do not know how long the protection induced by L1 VLPs will last. Will exposure to virus post-vaccination act as a natural booster? There is no unequivocal evidence for or against, but the preliminary indications from the trials are that this is probably not the case. It is assumed (and the natural infections in animals support this) that these vaccines will only be effective pre-exposure to virus. Genital HPV infection is usually sexually transmitted and immunisation must therefore precede the sexual debut, implying that the target population for vaccination will be 9–10-year-old prepubertal girls. This may be difficult for cultural and social reasons, particularly in developing countries.

The protection provided by the L1 VLP vaccines appears to be type specific. Thus immunisation with HPV 16 L1 VLPs protects against HPV 16 infection but not against any of the 34 other genital HPVs. Similarly, HPV 18 L1 VLPs protect against HPV 18 infection but not other HPVs. The current generation of VLP vaccines contain only HPV 16 and 18 and, assuming that HPV 16 accounts for 50–60% and HPV 18 10–12% of cervical cancer cases, even in the best scenario (with 100% vaccine coverage of the target population) only 60–70% of cervical cancers would be prevented. The cumulative prevalence of HPV types in cervical cancer is illustrated in Figure 1, and it is clear that increasing the number of types in the vaccine (e.g. 16, 18, 31, 45, 59) would prevent more than 80% of cancers, but to prevent more than 90% of cancers at least a further six types would need to be added.
Three questions are often posed about polyvalent HPV vaccines, namely:

1. If HPV types 31 and 45 and/or others are included as well as 16 and 18, will we get similar titres of antibody to each HPV type and achieve 80–90% prevention of cancer? The answer to this question is ‘probably yes’, since in a Phase I trial examining the immunogenicity and safety of an HPV 16/18/6/11 quadrivalent vaccine the vaccine recipients developed serum antibody to each VLP component and at comparable titres.4

2. Will we need different ‘cocktails’ of HPV types for different populations? There is no answer to this question at present. The HPV type distribution in cervical cancers is generally consistent worldwide but several reports using highly sensitive HPV detection and typing systems have found geographical variability.3

3. If we control types that are currently the most common, will other rarer types take their place? This is another unanswerable question at the present time but some indication may come from the Phase III trials of the 16/18 VLP vaccines. What is clear is that if the current HPV prophylactic vaccines are introduced for mass immunisation in countries with effective cervical cancer screening programmes, such as the UK, these programmes will have to continue unless significant cross-protection is induced by VLP immunisation (and this seems an unlikely scenario). However if vaccines including five or six types (e.g. 16/18/31/45/59) were to be licensed and vaccine coverage in the target population was high enough, this might prove sufficiently effective for screening to no longer be considered cost-effective.

Therapeutic vaccines

Whilst the development of prophylactic vaccination against HPV is exciting, realistically these interventions are at least a decade away. However, even if several decades must elapse before any effects will be evident, the need to develop effective immunotherapies remains a priority. The induction of strong, cell-mediated (as opposed to antibody) responses is certainly central to any therapeutic vaccine strategy and may be critical for long-term immunity in prophylaxis. It is important to define ‘therapeutic’ in this context and there are three possible scenarios:

1. A vaccine designed to be effective post-exposure to HPV.
2. A vaccine that could be effective against low-grade CIN.
3. A vaccine for high-grade CIN and cancer.

The antigenic targets in the first two scenarios might be identical but only the oncoproteins E6 and E7 are possible targets for the third scenario, since these are the only viral proteins that will be expressed in all high-grade lesions or cancer (Figure 2).

Post-exposure vaccines are worth more than a passing consideration. The communities with the highest incidence of cervical cancer are predominantly in the developing world, and in many societies immunising young girls before the sexual debut may not be easy for social and/or cultural reasons but immunising women who pose fewer problems. HPV testing, if adopted as the primary screening modality, could identify infection as opposed to clinical disease in many individuals; a post-exposure vaccine would have a place in the management of such women. In the dog and rabbit, immunisation with vaccines encoding E1 or E2 genes modified to increase antigen expression protects against challenge with live virus. Animals challenged with virus and subsequently immunised with an E2 vaccine either do not develop warts or established lesions regress, indicating that this may be both a post-exposure vaccine and immunotherapy for low-grade disease. These data from animal models have significant implications for the design of HPV vaccines and suggest that inclusion of an early protein such as E2 together with L1 would provide both prophylaxis and protection post-exposure and could be a second-generation vaccine.

High-grade and low-grade CIN should be considered separately when discussing therapeutic vaccines. Low-grade CIN is homogeneous and the lesions are genetically stable; in an immunocompetent individual an effective therapeutic vaccine such as an E2 vaccine should result in lesion clearance and no recurrence. CIN2/3 is heterogeneous, and the lesions are genetically unstable with the probability that immune parameters of importance will be disregulated. In view of this scenario it is distinctly possible that there will be a spectrum of responses to E6/E7 vaccination in patients with high-grade disease ranging from complete through partial to no clearance of the clinical disease – indeed this is what has been observed in the Phase I/II trials that have been carried out to date.5

Therapeutic vaccines for high-grade and malignant anogenital disease have been disappointing to date, and some significant scientific developments are needed if these are to have clinical utility.

Five-year view

HPV VLP vaccines have made cervical cancer, in theory, a preventable disease and the next 5 years should see the licensing of the first generation of these vaccines. All the evidence suggests that, for efficacy, the vaccines will have to be delivered prior to the sexual debut and, in
reality, this means that prepubertal girls will form the vaccinated population. The take up of such vaccines will depend upon social attitudes, public health policies and economics. Such a scenario prompts a number of currently unanswerable questions, namely: How well will a vaccine against a sexually transmitted agent which protects against a disease that may develop in 30 years’ time be accepted? How extensive will the coverage be if 9–10-year-old girls are the vaccinated group? And, finally, since vaccination might not mean the elimination of cervical cancer screening programmes, will governments and/or insurance providers pay for vaccination and screening?

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References

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