Immune control of human papillomavirus (HPV) associated anogenital disease and potential for vaccination

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Received 5 July 2004; accepted 7 December 2004

Abstract

This review discusses: (1) immune mechanisms relevant to the natural control of a human papillomavirus (HPV) infection; (2) viral strategies to evade or subvert immune attack; (3) the significance of immune escape as a feature of the evolution of invasive cancer; (4) vaccine strategies for prevention and/or therapy. HPV infection and associated malignancy can induce humoral and cellular immunity to capsid and oncoprotein viral proteins, but it is not always clear whether such responses are a consequence of the disease rather than the resolving factor(s). Prophylactic strategies are utilising virus-like particles (VLP) composed of the L1 viral capsid protein to induce neutralising antibodies, while therapeutic approaches are aimed at generating specific T cells targeted at the viral E6 and/or E7 oncoproteins. Thus far, HPV VLP vaccines have proved clinically efficacious in the early clinical trials to prevent infection. Different types of therapeutic vaccines including peptide, protein, DNA or viral vector encode have proved safe and immunogenic in patients, although there is often no correlation with clinical outcome. Understanding the equilibrium between viral and immunological factors will be important in providing the appropriate tools to evoke effective prophylactic and therapeutic immunity. It seems likely that combined prophylactic and therapeutic vaccine approaches could offer the best prospect for any significant reduction in death from cervical cancer worldwide.

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Keywords: HPV, Vaccines, VLP, E6 and E7 oncoproteins; Neutralizing antibodies; CTL

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Abbreviations: APC, antigen presenting cell; CIN, cervical intraepithelial neoplasia; CTL, cytoxic T lymphocytes; DC, dendritic cell; HPV, human papillomavirus; IFN, interferon; IL, interleukin; LC, Langerhans cell; LN, lymph node; MHC, major histocompatibility complex; NK, natural killer; ORF, open reading frame; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α; Th, T helper; VIN, vulval intraepithelial neoplasia; VLP, virus-like particles

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1. Natural HPV immunity

   The resolution of anogenital human papillomavirus (HPV) infection involves specific immune responses, as immuno-suppression in transplant recipients or patients infected with HIV is characterized by persistent dysplasia and increased risk for progression to malignancy (Sillman et al., 1997; Ferenczy et al., 2003). The relevant factors probably reflect the concerted action of tissue homeostatic, innate and adaptive immune components acting locally in the anogenital mucosa. The precise details of this process in the context of the natural history of HPV associated carcinogenesis are not fully understood.

   HPV infection is believed to occur through minor damage of the genital mucosa allowing access of the viral particles to target cells, probably the stem cells present in the basal layer. These cells and their progeny (transit amplifying cells) support episomal replication of the viral DNA with minimal viral gene expression (E1 and E2). The viral E6 and E7 products delay cell-cycle arrest and differentiation as epithelial cells move up from the basement membrane. The completion of the viral life cycle is intimately entwined with differentiation of the stratified squamous epithelium of the mucosa and essentially proceeds with little disruption of the epithelium, culminating in production of complete virions in the terminally differentiated cells of the outer layers (Zur Hausen, 2002; Doorbar, this volume).

   Protective immunity results from the interplay of non-specific innate immunity and antigen-specific adaptive immunity. The innate immune system senses tissue damage (danger) via signals from molecules, which would normally not be found extracellularly, including high mannose structures, heat shock proteins, DNA, RNA, etc. Sentinel cells, including epithelial cells, dendritic cells (DCs) (or Langerhans cells (LCs) in the skin), continuously sense the environment and coordinate with innate immune effectors (monocytes, macrophages, polymorphic leukocytes and natural killer (NK) cells) for the protection of mucosal tissues. This involves the production of immunoregulatory molecules including α-, β- and γ-interferons (IFNs), transforming growth factor-β (TGF-β), tumour necrosis factor-α (TNF-α) and interleukins (IL-1,-6,-10,-12 and -15) which can have direct controlling effects on virally infected cells-DCs or LCs in the cervical epithelium, are antigen-presenting cells with the unique ability to take up and process antigens in the peripheral blood and/or tissues. LCs provide the combination of MHC peptide presentation, costimulatory molecules (CD80, CD86 and CD40), cytokine production (e.g. IL-12 or IL-10) to activate specific naïve T cells and configure their terminal differentiation into effector cells (Niedergang et al., 2004). The integrated information acquired by the DCs can shape the subsequent T cell mediated immunity into T helper (Th) type 1 or type 2 or T regulatory response (Kalinski et al., 1999; Wang et al., 2004). A Th1 response will favour the production of cytotoxic T cell effectors which would be important in clearing any virally infected cells, while a Th2 response will facilitate the stimulation of B cells and their isotype switching providing for generation of neutralizing antibody. Immature DCs can also induce antigen-specific non-responsiveness or tolerance (Niedergang et al., 2004).

   The primary activated T cells against HPV antigens can control the initial pathogen challenge, but these die and there is differentiation of a subset (central memory), which provides for long-term memory (Kaech et al., 2002). It is believed that T cell recognition of HPV target antigens will be the key to the complete resolution of the infection. Investigation of human T cell responses to HPV oncoproteins in cervical neoplasia has largely focused on the activity in the peripheral blood and utilized several different assays, which have provided evidence of naturally occurring immunity. Thus, T helper (De Gruijl et al., 1998; Kadish et al., 1997), cytotoxic T lymphocytes (CTL) (Bontkes et al., 2000), γ-interferon ELISPOT (van der Burg et al., 2001a) and HLA tetramer (Voulte et al., 2000) based assays all show E7-specific activity at low systemic levels predominantly in patients with persistent HPV-associated lesions or cancers. A comparison
of peptide-specific responses in peripheral blood, local lymph node (LN) and tumour infiltrating lymphocytes from cancer patients indicated that HPV-specific CTLs are more abundant at the site of antigen exposure (Evans et al., 1997). A longitudinal study of CTL responses in women with HPV 16 infection and squamous intraepithelial lesions has implicated differential E6 responses in viral persistence (Nakagawa et al., 2000) an absence of which was also noted in carcinoma patients (Bontkes et al., 2000). Such HPV 16 E6-specific T cell immunity is frequently detected in healthy subjects and this is supportive of a role in protection against persistent HPV infection and associated development of malignancies (Welters et al., 2003). HLA-DR-restricted CD4+ tumour infiltrating lymphocytes specific for HPV 16 E7 have been detected in cervical cancer and these responses might be important for expansion of CTL effectors especially since HPV associated lesions do not invoke a strong local inflammatory response (Santin et al., 1999). Recent work from van der Burg et al. (2004) has shown that there is a reduced IL-5, γ interferon cytokine CD4 T cell responses to HPV oncogene peptides in patients with cervical cancer suggesting an absence of T cell help which could be critical to expansion of any CTL effectors in the absence of any local inflammatory response (Janssen et al., 2003).

Antibodies specific for the HPV 16 L1 major capsid protein have been detected between 4 months and 5 years after a primary infection (Carter et al., 2000), but some infected persons remain seronegative. It appears that seroconversion is slow and that antigenic exposure drives the process since it is associated with higher viral load and persistence of infection (Ho et al., 2004). Other studies have shown that HPV capsid-specific antibodies, elicited by natural infection, are not necessarily protective in subsequent infections, since seropositivity is not associated with a statistically significant decreased risk of re-infection with the homologous HPV type or genetically related types (Visci et al., 2004). Antibodies specific for E7 appear only with the development of cancer even though it is expressed in preneoplastic cells (Jochmus-Kudielka et al., 1989).

It is not possible to dissect the precise relevance of the above documented T and B cell responses to HPV antigens in human cervix infection and associated neoplasia with respect to clearance and/or protection versus further viral challenge. In cows, dogs and rabbits infected or immunized with their species-specific PVs there is development of neutralizing antibodies and resistance to further virus infection (Campo, 2002). Neutralising antibodies may be an effective way of preventing viral infection and spread, but cell-mediated surveillance of virally infected cells is likely to be important in the ultimate resolution of infection and disease. This is supported by evidence of T cell infiltration in regressing papillomas of man and dog (Arany et al., 1999; Nicholls et al., 2001). In addition, there is evidence from murine tumour models supporting a role for cytotoxic T cells against viral oncogenes in HPV tumour immunity (Frazer, 2004).

2. Viral strategies to evade or subvert immune attack

2.1. Low profile

The first viral strategy to avoid detection is to keep a very low profile. Thus, the HPV infection per se does not elicit any major damage likely to evoke the principle innate immunity danger signals. The virus infects only epithelial cells, encodes non-secreted proteins expressed at low levels, with virus production in cells, which are sloughed off at the end of their lifespan. There is no viraemia and the infected cells are not lysed, limiting the production of antigens for systemic presentation.

2.2. Viral gene expression on immune activation

It is increasingly clear that viral gene expression influences a variety of cellular functions not only to facilitate virus production in relation to the natural history of the epithelial differentiation, but also to hide from any local immunity. Several micro array approaches have shown that a principle target of high risk HPV E6 and E7 are the interferon responsive pathways of the infected epithelial cells (Nees et al., 2000; Chang and Laimins, 2000). In particular, HPV 16 E7 has been shown to bind to interferon regulatory factor 3 and inhibits its transcriptional activity (Barnard and Mcmillan, 1999) and HPV 18 E6 inhibits the JAK-STAT activation response (Li et al., 1999). Stat-1 is the primary regulator of the interferon response and thus HPV effects will modulate the direct and/or indirect effects of IFNs. These are the first line of defense in viral infections as they exhibit anti-viral, anti-proliferative and immunostimulatory functions. It is also apparent that these viral genes regulate other factors likely to influence the survival of virus infected cells including key chemokines like IL-8 and IP 10, which are important components of any local inflammatory response (Nees et al., 2000). Another strategy for immune evasion stems from the ability of HPV 16 E6 to down regulate the IFN-promoting factor IL-18 (Cho et al., 2001). Thus, activity of E6 and E7 provides the molecular basis for promoting viral persistence and avoiding innate immunity and the consequential activation of adaptive immunity. Other relevant influences include the modulation of antigen processing pathways through E5 mediated MHC expression (Zhang et al., 2003). The consequence of the modulation of these various local activation signals for the antigen presenting cells (APCs) will be to influence the polarization of Th cell types selected in the draining node since the subsets are biased by the first experiences of the DCs (Kalinski et al., 1999).

2.3. Activation and migration of T cell subsets

The number of LCs is significantly reduced in dysplasia and HPV infection (Connor et al., 1999). This may result in changes in cell surface E-cadherin expression in the basal and suprabasal layers. For example, E6 can down regulate
epithelial E-cadherin expression, which could modulate their contacts with LCs allowing suboptimal antigen capture and/or activation necessary for the initiation of anti-viral T cell responses. In addition, the change in tissue architecture is more permissive for the expansion and spread of immortalized and/or transformed cells (Matthews et al., 2003).

It is possible that HPV has evolved to exploit the endogenous tissue responses utilized by innate immunity to disfavor induction of a more threatening Th1 response which would favor the development of CTLs. Indeed, it has been shown that in cervical intraepithelial neoplasia (CIN) lesions there is a relative down regulation of TNF-α by the epithelium and upregulation of the Th2 cytokine IL10 compared to normal cervix (Mota et al., 1999). The migrating LC may thus be inappropriately activated, skewing any subsequent immune activation of T cells, which might include the induction of anergic or T regulatory cells (Kalinski et al., 1999).

Any useful generation and delivery of therapeutic cell mediated immunity demands a good local inflammatory response, which adequately and appropriately induces DCs to prime naïve T cells in the local LNs producing Th1 helper CD4 T cells to ensure optimal induction of CTL effectors. The details of clonal expansion of the T cells and development of long-lived memory T cells in the HPV disease are largely unknown, although the presence of HPV oncogene-specific CD4 responses has been reported (Santin et al., 1999). The potential importance of such responses in boosting CD8+ memory responses is well documented (Janssen et al., 2003). However, these cells may have negative consequences since certain cytokine profiles can produce immunosuppressive effectors, for example, to control autoimmunity (Shevach, 2000). Recent studies have documented a predominant Th2 polarity of tumour infiltrating lymphocytes in human cervical cancer (Sheu et al., 2001) and the draining node appears to have an increased proportion of T regulatory cells (Fattorossi et al., 2004).

2.4. Immunogenetics of HPV disease

The recognition of foreign peptide antigens by T cells is restricted by the polymorphic products of the MHC classes I and II. The natural processing of viral proteins in vivo results in the production of many different peptides presented in conjunction with MHC molecules on the surface of the cell. The HLA molecules expressed by an individual restrict the repertoire of peptides presented. The class I HLA-A, -B and -C loci are expressed by most somatic cells and generally present endogenously processed peptides to CD8 T cells. The class II HLA-DR, -DQ and -DP are primarily expressed by antigen-presenting cells like DC and can present exogenous and endogenously processed antigen to CD4 T cells. The MHC molecular expression is usually upregulated by cytokines associated with an inflammatory response, so this will be suboptimal in an HPV infected target cell. However, the genetics of HLA may also influence susceptibility to HPV infection or ability to clear the virus and thus avoid persistence, which is the key risk factor for progression (Little and Stern, 1999; Hildesheim and Wang, 2002).

2.5. HPV driven anogenital neoplasia: integration of viral and immune factors

It is interesting to consider that although there is evidence that HPV infection and associated malignancy can induce humoral and cellular immunity to capsid and oncogene viral proteins, it is not known whether such responses are a consequence of the disease rather than being the critical resolving factors. The majority of apparently immunocompetent individuals infected with HPV are able to clear the infection with no further consequences, but persistent infection is correlated with progression of cervical disease (Steenbergen et al., this volume). Such persistent infections may result from viral stealth and immune interference strategies leading to escape from the normally effective immunity. Any interference with local APC of the cervix may protect the infected tissue from the attentions of host immunity. Overall it seems likely that the evolution of HPV has produced a pathogen which survives by a combination of stealth and specific interference with innate immunity, with knock-on effects on adaptive immunity which in themselves advantage the infection.

3. Immune escape as a feature of the evolution of invasive cancer

It is clear that HR-HPV E6 and E7 are the predominant transforming proteins, via their interaction with cellular tumour suppressor gene products p53 and pRb, respectively. In initial infection, HPV is present as an episome, but in the majority of more advanced lesions and invasive tumours HPV is integrated into the host genome (Wentzensen et al., 2004). This leads to inactivation of the E2 open reading frame (ORF) and loss of its repressor function for E6 and E7 transcription. This provides the opportunity for the accumulation of genetic changes in a multistep process that can result in the development of cancer, usually over a period of 1–2 decades (Duensing and Munger, 2004). This presents new hurdles for the natural immune response and immunotherapy since, in addition to the mechanisms outlined above, further immune escape may result from selection as part of the multistep events in carcinogenesis of the lesions. Thus, in some progressive cervical lesions, the immune system may not be triggered until after HPV integration and other cellular events have occurred, compromising the relevance of such immunity in resolving a malignant lesion. For example, CTL might drive the selection of immune-resistant tumour cells. The high frequency of HLA class I down-regulation seen in anogenital neoplasia (Keating et al., 1995) and associated with progression (Bontkes et al., 1998; Abdel-Hady et al., 2001) are consistent with such immune escape mechanisms acting at the target cell level. Detailed molecular analyses of
Fig. 1. Immune response in HPV anogenital neoplasia.
cervical carcinomas have shown that these HLA class I dysregulations result from multiple genetic mechanisms (Brady et al., 2000) and occur in around 90% of tumours (Koopman et al., 2000). Fig. 1 summarizes some of the key components of the viral cellular and immune interactions through the spectrum of neoplasia.

4. Vaccine strategies for prevention and/or therapy

The causal link between HPV infection and malignant transformation in cervical neoplasia provides a unique opportunity for both prophylactic and therapeutic vaccination. Cervical screening is unavailable in most of the developing world, which has the highest cervical cancer mortality. Vaccination may offer a more feasible solution to combating HPV associated neoplasia.

4.1. Prophylactic vaccines

The major breakthrough in HPV vaccine technology was the demonstration that viral capsid proteins have the intrinsic capacity to self assemble into virus-like particles (VLPs) (Zhou et al., 1991; Kirnbauer et al., 1992). These are morphologically similar to infectious virions, present conformational epitopes that are highly immunogenic, but lack viral DNA. Safety and immunogenicity trials in healthy volunteers have been done with HPV 16 L1 VLPs produced from baculovirus infected insect cells (Harro et al., 2001) and from yeast (Koutsky et al., 2002). These have established that the vaccines are well tolerated and generate strong immune responses that are several orders of magnitude higher than those exhibited by naturally infected populations. Interim analysis of an HPV 16 L1 VLP vaccine produced in yeast showed proof of principle efficacy in a study of over 1500 women HPV negative at recruitment and receiving either the HPV 16 VLP vaccine (immunizations at 0, 2 and 6 months) or placebo (Koutsky et al., 2002). A trial of a baculovirus derived HPV 16 and 18 VLP vaccine formulated with 3-deacylated monophosphoryl lipid A and aluminum salts compared to a placebo control in young women who were seronegative for HPV 16/18 and high risk HPV DNA negative at recruitment has recently been reported with similar immunogenicity and safety results (Dubin, 2004). These results are very encouraging, but there are still challenges ahead for the implementation of an effective vaccination strategy for prevention for HPV associated disease (Baseman and Koutsky, this volume).

Current clinical trials aim to demonstrate that the vaccines not only prevent infection but also the development of intermediate and high grade CIN (Schiller and Davies, 2004). One scenario for implementation of widespread vaccination would be to target immunization of adolescent girls prior to their first sexual encounter, but this could be controversial. It is obvious that one cannot ignore men in such strategies, but the value of any vaccination of males is completely unknown and there is very little known about the natural history of HPV infection in men (Bleeker et al., 2002). The agenda for implementing widespread prophylactic vaccination must clearly take account of the characteristics of the populations with respect to the current screening programmes, disease incidence and treatment options. It is clearly not possible to consider all these aspects in a single clinical trial or longitudinal study. Several studies, which use decision analytical approaches with mathematical simulation models, have been published which begin to consider the factors which are important to properly evaluate and quantify public health benefits of any potential HPV vaccine (Goldie et al., 2003). Recent modeling has indicated that vaccination could be cost effective in reducing cervical cancer rates in conjunction with PAP screening if age of first screen and the screening intervals were raised (Goldie et al., 2004).

4.2. Therapeutic vaccines

Overall, it is clear that T cells can recognize viral oncogene antigens in patients exposed to HPV infection, but their precise role in control of infection of transformed cells has not been established. There are substantial numbers of publications describing preclinical model studies of vaccines based on oncogene peptides or proteins, DNA plasmids and different viral vectors (Frazer, 2004). Here, a few examples of those which have made it into phases I and II clinical trials will be outlined.

4.2.1. Peptides or recombinant proteins

It is possible to predict immunodominant or subdominant peptides of viral antigens that would associate with particular HLA alleric products and are recognized by human T cells. Since 40% of Caucasians carry the HLA-A2 allele, HPV 16 E7 peptides presented by this allele have been the immunogen in several phase I/II peptide-based clinical trials (Steller et al., 1998; van Driel et al., 1999; Ressing et al., 2000; Muderspach et al., 2000). The advantages of the peptide approach are cost effectiveness, as peptide vaccines are cheap to produce and immunological responses following vaccination are relatively straightforward to measure. A recent study demonstrated that vaccination with longer peptides (22–35mer) with DC activating agents generated both CD4 and CD8-specific T cell responses against HPV oncocenes and resulted in more vigorous CD8 CTL responses than vaccination with exact minimal CTL epitope length (Zwaveling et al., 2002). A clinical trial is underway in patients with HPV 16 associated neoplasia.

Recombinant proteins have the advantage over peptide approaches in delivery of all potential epitopes to the antigen processing cells of the immune system. Such vaccines can be administered regardless of the individual’s tissue type, as APCs of the immune system process and present one or more peptide epitopes in association with host HLA molecules. The challenges involve the production and purification of the viral proteins including fusions with molecules like heat shock proteins and their formulation with appropriate adjuvants in...
order to elicit the necessary processing and subsequent acti-
vation of T cells (Frazer et al., 1999; Goldstone et al., 2002;
Barnden et al., 2004). A variation is delivery with ex vivo
prepared DCs (Adams et al., 2001; Santin et al., 2002). Over-
all the experience from the various polypeptide vaccines is
that they are apparently safe, but immunogenicity has only
been shown in a fraction of patients and does not correlate
with limited clinical outcome data (Frazer, 2004).

4.2.2. Plasmid DNA vaccines

It would appear that plasmid DNA encoding an antigen
offers significant advantages for the preparation, formulation
and delivery of a vaccine. A further embellishment is the
use of encapsulation in a biodegradable polymer micropar-
ticle format, which potentiates delivery to APCs. Garcia et
al. (2004) assessed the safety and efficacy of an encapsulated
plasmid-DNA-encoding fragments derived from the E6 and
E7 proteins of HPV-16 and -18 in a multicentre, double-blind,
randomized, placebo-controlled trial of patients with hystery
confirmed CIN2/3. However, the claimed putative vaccine-
induced effect in younger women showed no specificity for
HPV-16- or HPV-18-positive lesions. Non-specific immune
stimulation via CpG sequences in the vaccine-DNA lead-
ing to activation of plasmacytoid DC, via Toll-like receptor
9 (Kaisho and Akira, 2003) and/or immune cross-reactivity
may have played a role in clinical outcome. It is vital that
appropriate T cell functional assays are performed in such
studies to confirm that there is a mechanistic action consis-
tent with the rationale.

4.2.3. Viral vector vaccines

The most extensively tested HPV vaccine vectors are those
based on recombinant vaccinia. The advantage of these vac-
cines is that HPV proteins are endogenously synthesised from
viral DNA by host cells, with the result that an array of HPV
peptides are produced, processed and presented on the cell
surface in conjunction with MHC class I molecules. Such
a system poses no restriction on patient HLA genotypes or
CTL repertoire and allows several HPV types or antigens
to be included in the vaccine. A live recombinant vaccinia
virus encoding HPV 16 and 18 E6 and E7 (TA-HPV) was
given to eight patients with advanced cervical carcinoma and
in a subsequent multicentric EORTC phase II trial, it was
administered to early stage cervical cancer patients and im-
une responses measured before and after immunization.
These studies established the safety and immunogenicity of
the vaccine in at least a proportion of those patients vac-
cinated (Borysiwicz et al., 1996; Kaufmann et al., 2002).
TA-HPV has also been used in the treatment of high grade
vulval intraepithelial neoplasia (VIN) because this disease
often presents as a chronic problem unresponsive to stan-
dard ablation treatments (Davidson et al., 2003). There was
some but not complete correlation between HPV immunity
and clinical response defined by lesion shrinkage at 24 weeks
post-vaccination. Importantly, the best correlation to respon-
siveness was to local immune infiltration. Prior to vaccination,
clinical responders had significantly higher levels of lesion-
associated CD4+ and CD8+ cells than non-
responders. It appears that local immune status may be a
critical factor in potential responsiveness to vaccine therapy
in HPV-associated neoplasia and should be carefully mon-
tored in future placebo-controlled trials of immunotherapy
for VIN.

4.2.4. Prime-boost strategies

Prime-boost strategies utilising a priming immunisation
treatment (e.g. DNA plasmid or viral vector or protein) followed by
a heterologous boost with a different viral vector encoding
the immunogen are very effective in several models of viral,
parasite or tumour antigen vaccination (Woodland, 2004).

Another vaccine formulation that has been tested in humans
is a fusion protein of HPV 16 L2E6E7 (TA-CIN) and this was
well tolerated when given to healthy volunteers and induced
antibody and proliferative responses against TA-CIN, plus
γ-interferon ELISPOT responses to HPV 16 oncoproteins
(de Jong et al., 2002). In the preclinical studies, the het-
erologous prime-boost immunisation strategy of TA-CIN
with TA-HPV showed enhanced immunogenicity compared
with either agent alone, but the order of TA-CIN followed
by TA-HPV was superior to the reciprocal as defined by
the induction of T cells against the oncoproteins (van der
Burg et al., 2001b). Priming with TA-CIN is likely to focus
the immune response to the oncoprotein when boosting
with TA-HPV. This regimen has now been tested in patients
with anogenital intraepithelial neoplasia (Smyth et al.,
2004). While this prime-boost regimen induces cellular
immunity in VIN patients, there is no simple relationship
between induction of systemic HPV16-specific immunity
and clinical outcome. Other factors that may play a role in the
eradication of long-term established VIN lesions need to be
determined.

4.3. Prophylactic and therapeutic vaccination strategies

The early results of therapeutic vaccine trials have deliv-
ered limited information, which might not be surprising from
our knowledge of the natural history of the immune response
to HPV oncoproteins and the related cellular changes which
compromise the spectrum of immune surveillance in this
disease. Judging the usefulness of therapeutic vaccine treat-
ment for HPV associated malignancy must await the results
of more extensive trials that assess and confirm clinical effi-
cacy and the underlying immunological mechanisms. How-
ever, therapeutic vaccination may be useful in treatment of
premalignant lesions in conjunction with prophylactic strate-
gies. It has been shown that VLPs can activate DC and HPV
16 VLP-E7 chimera vaccines can generate useful T cell re-
sponses to E7 (Greenstone et al., 1998; Schafer et al., 1999)
as well as neutralizing antibodies to viral capsids. This ap-
proach could provide a means to effectively treat incident
HPV infection. The risk for cancer development from long-
term HPV infection could be managed with local treatment,
and immunization in these patients, but as is presumably the case now, most individuals would develop effective natural immunity.

Acknowledgement
I thank Becky Stern for preparing Fig. 1.

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