Much progress has been made in the prevention and therapy of premalignant and malignant dysplasia caused by human papillomavirus by encouraging screening programs and recently by introducing preventive vaccines. To further reduce the worldwide burden of HPV-associated cancer supplementation of the established therapies with immunotherapeutic methods would have the potential for significant impact.

Dysplastic epithelial lesions and cancer of the anogenital and the oropharyngeal region show strong association with HPV. Therefore cervical carcinoma and HPV-associated squamous cell carcinoma of the head and neck differ from most other malignancies in that they harbour HPV-derived antigens. Expression of the viral oncoproteins is mandatory to maintain the cancerous phenotype.

These antigens are unique to the tumour and attractive targets for "proof of concept" studies in the development of therapeutic vaccines showing the general applicability of tumour vaccination and prove the correlation of immune response and clinical response. To date numerous clinical trials have been performed with candidate vaccines predominantly testing the efficacy for cervical cancer and its precursors. Although a naturally induced anti-HPV T cell response in patients was shown, clinical success of therapeutic vaccines was sparse. This may be attributed to immunosuppression, immunoselection, and immunoediting by the tumour cells.

Factors of the individual that led to the failure of autonomous clearance of the initial infection may also contribute. Overriding this failure, reversing immunosuppression and application of vaccines in early stages of the disease is the key task for the future. The aim of this article is to summarize recent developments of therapeutic vaccines and discuss obstacles that hinder their success.

Key words: human papilloma virus; immunotherapy; therapeutic vaccine; immunomodulation; clinical trials, immunoevasion; cervical cancer; squamous cell carcinoma of head and neck;

INTRODUCTION

Cervical cancer and subgroups of anal carcinoma and squamous cell cancer of the head and neck (SCCHN) are associated with high-risk Human Papillomavirus (HPV) infection, creating a unique opportunity to prevent and treat these malignancies by anti-viral vaccination.

HPVs are a family of double-stranded DNA viruses with over 100 different genotypes. HPV genotypes are divided into low-risk and high-risk for their potential to transform epithelial cells. Fifteen HPV types are classified as high-risk types, 3 are classified as probable high-risk types and 18 are classified as low-risk types. Low-risk HPV types induce benign genital condylomata and low-grade squamous intraepithelial lesions, but also can induce papillomatosis in the oral cavity, or pharyngeal and laryngeal regions. The high-risk HPV types are associated with invasive cancers. In 99% of cervical cancers high-risk HPV can be detected with type HPV16 found in about 50% of cases. A variable but significant proportion of cancers at other mucosal sites show association with high-risk HPV infection and in average 18% of SCCHN contain DNA of these types. In general, about 75% of the sexually active population acquires at least one genital HPV type during lifetime. Due to an active immune response, most individuals remain asymptomatic and clear HPV infections spontaneously within approximately 8-18 months. A small percentage of individuals fail to clear the infection and then are at high-risk for developing dysplasia. This risk differs significantly between different viruses. HPV16 and HPV18, as the predominant high-risk HPV types, are leading to high grade precancer in around
20% of persistently infected persons over 10 years course of time. Other high-risk HPV types have a lower potential of about 1.5% to induce malignant lesions. But also in low-risk HPV infected persons a chance of 0.5% remains to develop a malignancy over time. Individual host factors may contribute to virus persistence and lesion progression but are yet not sufficiently defined and understood. Certainly, genetic factors and polymorphisms of an individual are important. They may influence the immune response like the capability of antigen processing and presentation by an individuals MHC genetic make-up, the T cell receptor repertoire, or the ability to respond to proinflammatory signals conveyed by toll-like receptors (TLRs). Other genetic polymorphisms may modify the way viral oncoproteins bind to and inactivate cellular target proteins. HPV genome variants are common. For example E6 binds and inactivates p53, the "guardian of the genome".

Population studies conducted in Europe, Asia and the Americas identified more than 20 amino acid changes within the HPV16 E6 oncoprotein when compared to the "wild-type" or "prototype" sequence. This HPV16 sequence was the first to be published and was isolated from an European woman diagnosed with cervical cancer. Later on it became apparent that several variant HPV16 genomes exist worldwide and that these are linked to certain geographic areas. E6 variants contain single or multiple amino acid changes. The most frequently detected variants in HPV16+ cervical cancer contain changes in residues 10, 14, 78, and 83 of the E6 protein and may interfere with p53 inactivation. Also the polymorphisms altering the activity of cellular detoxifying enzymes like methylene-tetrahydrofolate reductase, or cytochromes P450 were discussed. Such factors were investigated, however, conclusive studies are lacking.

Failure to clear HPV infection leaves host cells under the influence of the viral oncoproteins. Persistently infected persons can develop clinically or histologically recognizable precancers that can persist and may progress over time into invasive cancer.

Prophylactic vaccines have been proven highly efficacious. They are being introduced since 2006 and have the potential to reduce the burden of cervical cancer by approximately 70% and also the vaccine-type related precancers. They have, however, no therapeutic potential due to their mechanism of action via virus-neutralizing antibodies targeting the L1 capsid antigen which is not expressed in persistently HPV-infected basal epithelial cells. Therefore, therapeutic vaccines may still offer benefits for the treatment of high grade lesions (or worse) which will still develop despite the availability of prophylactic vaccines because i) prophylactic vaccines do not protect against all carcinogenic HPV types, ii) lesions in individuals already infected today might still progress to cancer if left untreated, iii) when protective immunity fades breakthrough infections may arise, and iv) not everyone will be vaccinated.

At this point it should also be taken into account that prophylactic vaccination will not cover all individuals since it is recommended mainly for girls and young women. For the time being prophylactic HPV vaccines are not recommended for boys and men in most countries mainly due to lack of efficacy studies and cost benefit analyses.
However, a proportion of cancers at extragenital sites arise equivalently in both sexes. This is exemplified by HPV-associated SCCHN that can arise in both genders.

**SIGNIFICANCE OF HPV IN CERVICAL CANCER**

Despite widely available effective screening programs, cervical cancer remains the second leading cause of cancer deaths in women worldwide.

Cervical precancers can be detected by cervical cytological screening (using Papanicolaou smears), which has successfully reduced the mortality rate from cervical cancer in developed countries. True precancers, so-called high-grade cervical intraepithelial neoplasia (CIN) have to be removed surgically. Removal of part of the uterine cervix can have an adverse effect on pregnancy outcomes resulting in an increased risk of premature and low birth weight in future pregnancies. This effect is independent on the surgical technique used. In contrast, cytologic screening, prophylactic and therapeutic vaccination have the potential for primary and secondary prevention. In addition, therapeutic vaccination would not lead to loss of cervical tissue. Most importantly, vaccination concepts are especially attractive for developing countries where screening programs are minimal, and cervical cancer remains the second leading cause of cancer-related deaths among women.

**SIGNIFICANCE OF HPV IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**

Oral HPV infections are less common than cervical infections in women and they are more frequent among women with a cervical HPV infection. The majority of these women does not have simultaneous oral and cervical infections by the same HPV type. Yet interestingly, the number of women who does is statistically significant indicating that the oral and cervical reservoirs for HPV infection are likely not entirely independent of one another.

SCCHN accounts for approximately 6% of all cancers cases and for about 650,000 new cases and 350,000 deaths world wide each year. In spite of this burden there is no screening program established for oral HPV infection or HPV-induced oral dysplasia.

While early-stage SCCHN can be treated relatively effectively, fewer than 40% of patients with advanced, metastatic disease can be cured. Unfortunately, about two-thirds of patients with SCCHN present with advanced stage disease, commonly involving regional lymph nodes. Distant metastasis at initial presentation is found in about 10% of patients. The 5-year survival for all stages is about 60%.

Despite significant improvements in surgery, radiation and chemotherapy, long-term survival rates in patients with advanced stage SCCHN have not significantly increased in the past 30 years. Two distinct causes of SCCHN are known. Traditionally, SCCHN is linked to tobacco and alcohol abuse. A second etiology defines a subset of SCCHN that is associated with infection with high-risk HPV types 16 and 18. HPV16 is found in about 90% of the these specific lesions and therefore is the predominant type. High-risk HPV infection has been detected in 20% to 30% of tumours located in all head and neck anatomic subsites. About 50% of the tumours that arise in the oropharynx especially in the tonsil and the base of tongue are high-risk HPV positive.

For laryngeal cancer the role of HPV is less clear, data on the prevalence of high-risk HPV associated SCCHN vary and multicenter studies have not been performed yet. Supraglottic laryngeal cancer is more frequently associated with high-risk HPV than other anatomic sites in the larynx.

Taken together, HPV infection has been demonstrated to be a risk factor for SCCHN. Patients that have detectable anti-HPV16 antibodies are at a 2.1 fold higher risk to develop SCCHN in general and at 10.2 fold higher risk to develop squamous cell cancer of the tonsil. Other risk factors found were, similar to those for cervical cancer, sexual promiscuity and early first sexual contacts. It is therefore discussed that HPV-associated SCCHN should be classified as sexually transmitted disease. This is especially interesting in the context that the frequency of alcohol and tobacco induced hypopharyngeal and laryngeal squamous cell carcinoma is decreasing in developed countries while the incidence of HPV-associated squamous cell carcinoma of the tonsil is increasing. Other studies found a lower rate of carcinogenic risk factors and p53 mutations in a younger patient population that is less exposed to chemical cocarcinogens as well as p16 expression that is a marker for high-risk HPV oncogene activity. Whether this also contributes to prognosis is unclear. This suggests that unique factors may be associated with viral entry, propagation/transformation and immune evasion in these patients.

Currently, screening for high-risk HPV in SCCHN is not performed on a routinely basis. There is mounting evidence of a distinct clinical behaviour of these tumours that may require specific treatment strategies. Therefore, all future clinical studies should separate systematically the two etiologies (HPV-associated/non-associated) for SCCHN to identify differences in responses to treatment and in follow-up. A reduced risk of relapse and secondary tumours is associated with high risk-HPV positivity of oropharyngeal cancer as well as for therapeutic response and survival. Compared to tobacco-related SCCHN, HPV-associated SCCHN are less differentiated and are more prone to metastasize to the neck when the primary tumour is still small at time of detection. The prognosis of HPV-related oropharyngeal cancer is more favourable than HPV-negative SCCHN. This is the case in terms of overall-survival as for disease-specific survival. The underlying causes, however, remain unknown.

Possibly an immunological bystander effect supports clinical treatment and provides a rationale for immunotherapeutic targeting of HPV-associated SCCHN.

Some studies have characterized endogenous T cell immunity to HPV-encoded oncoproteins, E6 or E7, in SCCHN patients. In these studies it was found that infection
with HPV16 significantly alters the frequency and functional capacity of virus-specific T cells in SCCHN patients. The immunogenicity of HPV16-encoded antigens was defined as critical factor for the development of vaccine-based strategies for enhancing antitumour immunity in patients with HPV+ tumours.

In addition to the presence of HPV-specific effector T cells, successful tumour elimination requires that HPV-infected tumour cells function as appropriate targets for CTL recognition and elimination. Immunohistochemistry of HPV16+ SCCHN tumours showed that the antigen-processing machinery components are downregulated in tumours compared to adjacent normal squamous epithelium. Thus, immunity to HPV16 E7 is associated with the presence of HPV16 infection and presentation of E7-derived peptides on SCCHN cells, which show evidence of immune escape. These findings support further development of E7-specific immunotherapy and strategies to enhance the antigen-processing machinery component expression and function that are likely to result in improved cytotoxic T lymphocyte recognition and may need to be incorporated into T cell-based immunotherapy against this disease.

STRATEGIES FOR THERAPEUTIC VACCINATION

While prophylactic vaccines employ sturctures of the viral capsid to induce anti-viral immunity, therapeutic vaccines target antigens present inside the infected cell. The predominantly targeted antigens are the HPV onco-genes E6 and E7. Their sustained expression is required for the maintenance of the cancerous phenotype. Several therapeutic vaccines evaluated in clinical trials over the past 15 years target the E2, E5, E6 and/or E7 proteins by many different strategies. These vaccines activate the patient’s cellular immune response to recognize and kill cells that express, process and present HPV proteins. The cellular immune system consists of several cell types like Natural Killer cells and cytotoxic T lymphocytes that are able to specifically recognize virus-infected or transformed cells. It is believed that the cytotoxic T cells are the most important defence against tumour cells as well as virus-infected cells because of their ability to specifically recognize peptide antigens derived of viral or mutated cellular gene products. The aim of therapeutic vaccines is therefore to activate and increase the number of this class of lymphocytes.

Initial trials in patients with advanced cervical cancer, who tend to have decreased immune function showed vaccine safety. In more recent and ongoing immunotherapy trials patients with earlier invasive or premalignant disease were included. Patients with lesions induced by mucosal or cutaneous HPVs such as cervical and vaginal intraepithelial lesions, anal intraepithelial lesions, condylomata and anogenital warts, head and neck squamous cell carcinomas and recurrent respiratory papillomatosis were treated. These trials are placebo-controlled, blinded, with higher patient numbers and less immunosuppressed individuals. This facilitates interpretation of antigen-specific immunity and its correlation to clinical efficacy. Performing therapeutic vaccination trials in patients with precancerous lesions will need a very close monitoring when lesion development is to be observed for longer periods of time. To participating patients an effective definitive treatment is withheld that is, on the other hand, not without side effects and is probably an overtreatment in many of the patients that could experience spontaneous lesion regression. Therefore, performing such vaccination trials is not unethical.

In addition, the choice of antigens is changing: initially and for pragmatic reasons the HPV E7 protein was regarded as ideal target. Recently it was shown that the larger E6 and E2 proteins may be more immunogenic and more effective targets.

Also new basic immunology findings such as the presence and characterization of immunosuppressive regulatory T cells have influenced the strategies of immunotherapy.

Since the local tumor environment is immunosuppressive or not immunostimulatory a combination of vaccination with topical immune stimulatory agents such as Imiquimod or other proinflammatory mediators like interferons may improve the performance of systemic immunization by vaccines.

CLINICAL TRIALS WITH EXPERIMENTAL THERAPEUTIC HPV VACCINES

Vaccination strategies used to target HPV proteins in clinical trials were mostly based on peptides/proteins, viral vectors, DNA, or dendritic cells. For example, Muderspach and colleagues vaccinated women with high-grade vulvar intraepithelial neoplasia (VIN) with two minimal T cell epitopes of the HPV16 E7 antigen in four escalating doses emulsified in Freund's adjuvants. Only 3 of the 18 patients cleared VIN until 3 weeks after the last immunization. Partial regression was observed by colposcopy in 6 additional patients. Immunological responses were detected in 10 of 16 patients. Virus DNA clearance in cytological samples was detected in 12 of 18 patients, however, in biopsies viral RNA was still detectable. The short follow-up period may have prevented better regression results.

The recombinant protein HspE7, a fusion of heat shock protein 65 (Hsp65) from Mycobacterium bovis and HPV16 E7 has shown clinical responses when administered to patients with cervical and anal precancerous lesions. Patients with recurrent respiratory papillomatosis, who were treated with HspE7 after debunking surgery had a significantly extended time until repeat surgery.

A very attractive approach of vaccination uses long overlapping peptides as antigen. These synthetic peptides represent the complete antigen in several fragments. They are taken up by antigen presenting cells, are then processed to the respective minimal T cell epitopes, are loaded onto the MHC and presented to T cells. Ideally, such activated T cells will find the corresponding naturally processed and presented epitopes on the tumour cells and are activated to exert their cytolytic function.
In humans, peptide vaccines have the disadvantage that the diverse HPV types causing the disease have to be known. Long peptide vaccines at least circumvent the necessity to know the patients HLA type what is obligatory for minimal epitope peptide vaccines.

In a phase I study end stage cervical cancer patients were treated 4 times at 3 week intervals with different combinations of HPV16 E6 and/or E7 long peptides adjuvanted with Montanide ISA-51 by s.c. injections. While all combinations were well tolerated and toxicity was not beyond grade 2, no clinical response was seen in these progressed patients. Importantly, strong T cell responses characterized by IFN-gamma secretion were found by ELISPOT analyses which were dominated by specificity for HPV16E6. Both CD4 helper and CD8 cytotoxic T cells were induced and detectable up to 12 months after the last vaccine application. Although most T cells were of a helper effector type 1 phenotype also potentially immunosuppressive regulatory T cell phenotypes were expanded potentially hampering effectiveness of the vaccine. T cells recognized a broad number of epitopes underlining the immunogenicity of the approach and the potential of this type of vaccine. However, it was noted that the depletion or inactivation of the regulatory T cells may be a necessity for successful immunotherapy against HPV-induced cancer.

Recombinant protein technology takes advantage of the ability of truncated L1 proteins to form virus-like particles (VLP) identical to the manufacturing techniques for prophylactic vaccines. Heterologous antigens can be fused to the truncated L1 and are incorporated into the particles now termed chimeric virus-like particles (CVLP). CVLPs show high prophylactic and therapeutic efficacy in animal models and immunogenicity in humans, where they induce cytotoxic CD8+ T cells to E7. We have used a CVLP consisting of HPV16 L1 fused to amino acids 1-55 of HPV16 E7 in a placebo-controlled, blinded phase I/II clinical trial. Thirty-six patients with CIN 2/3 lesions received 4 applications, and were equally randomized to receive placebo or 2 different dosages of the vaccine. The vaccine was safe and well tolerated at both dosages with minimal side effects comparable to the prophylactic vaccines. Importantly, the CVLP vaccine induced high antibody titers to the L1 and also to E7. The response followed an anamnestic pattern in these actively HPV16 infected patients. T cell responses to L1 were measured in 90% of patients while induced or enhanced T cell responses to E7 were found in 50% of the vaccinees. Although not statistically significant, due to low numbers of patients, there was a clear trend for clinical improvement in the vaccine versus the placebo group. Histological improvement was observed in only 25% of placebo recipients, but in 39% of vaccinees, and 56% of these were free of HPV DNA by the end of the study. Since the vaccine was not adjuvanted with additional immunostimulatory agents there is room for improvement.

As an example for a recombinant virus a vaccinia-based vector, termed TA-HPV, expressing mutated HPV16 E6/E7 and HPV18 E6/E7 was given to cervical cancer patients with early invasive disease around surgery. Safety, tolerability and immunogenicity were acceptable. In addition, the vaccine was tested in conjunction with protein-based strategies in order to circumvent any anti-vector immunity by heterologous prime-boost immunization.

Dendritic cell-based therapies and more recently DNA-based therapies will not suffer from such difficulties. Preexisting or induced immunity is not expected to pose a problem. Both strategies are still being pursued. Despite very promising preclinical results with dendritic cell-based vaccines the current data of clinical trials underline the problem of immune evasion and immune suppression in patients with advanced cervical cancer. Obstacles to be solved are the compromised antigen presentation by loss of HLA expression or components of the antigen processing machinery, the strongly immunosuppressive cytokine micro environment within the tumor, and the recruitment of immunosuppressive cells like regulatory T cells. Only when solving these specific problems by combination therapies such as tumour debulking, reversion of immune evasion, and a powerful immune stimulation this strategy can possibly be successful in late stage patients. It will, however, inherently have the disadvantage of a highly individualized therapy.

A strategy for a relatively cost effective and stable vaccine may be the development of DNA vaccines. Initial clinical trials have shown their safety and that they are well tolerated, but the immunogenicity of DNA vaccines in larger animals and humans was disappointing in clinical trials and objective tumour or clinical responses were rare.

The concept of DNA vaccines is the uptake of eukaryotic expression plasmids into cells and expression of an encoded antigen to which an immune response is then induced. Advantages that DNA vaccines potentially have are (i) full-length cDNA of a given antigen provides all potential epitopes overcoming the limitations of MHC restriction (ii) plasmid DNA is inexpensive to produce and easy to purify (iii) the plasmid DNA produced in bacteria contains unmethylated CpG motifs that act as potent immunological adjuvants (iv) plasmid DNA is stable and can be conveniently handled and distributed also without cold chain what is important for developing counties (v) the safety of DNA vaccines has been demonstrated and only few mild side effects were observed, and (vi) no preexisting immunity or anti-vector immunity to plasmid DNA-based vaccines are seen enabling repetitive booster vaccination.

Viral oncopgenes like HPV E6 and E7 as vaccine genes in DNA vectors carry the potential for transformation of cells due to their oncogenic activity. It is a mandatory prerequisite to inactivate this transforming activity. To this end, we have developed a generic strategy by reorganization of the genetic sequence termed "shuffling", i.e. dissection of the original sequence of the E7 gene at known sites responsible for transforming activity and fusion of the fragments in a "nonsense" order. Thereby, all putative HLA epitopes are still contained. We could show that the
rarranged primary sequence was devoid of transforming properties and induced E7-specific cytotoxic T lymphocytes in mice and in humans after in vitro immunization77. Immunogenicity of the sequence was significantly enhanced by codon optimization and by adding a Kozack sequence for more efficient translation in human cells.

Another study tested the efficacy of a DNA-based vaccine against a human HPV16+ esophageal squamous cell carcinoma cell line in a xenograft model by engrafting immunocompetent human peripheral blood lymphocytes into SCID mice. This study suggests that prophylactic vaccination delayed tumour growth through CD8+ T cell-dependent apoptosis78. Future and current clinical trials will show if this translates into DNA vaccine efficacy.

**FUTURE DEVELOPMENTS**

Continuously, novel strategies targeting HPV-induced malignancy advance the field of cancer immunotherapy significantly. Whether also clinical benefits will result from these studies has to be seen.. "Proof of concept" studies on the development of therapeutic vaccines by using HPV-induced malignancies has obvious advantages. HPV derived tumor antigens are well defined. Compared to tumor-derived self-antigens, the HPV-antigens elicit strong natural and induced immune responses. Moreover, the inherent problem of immune evasion can be studied. The progress that has been made in the development and introduction of prophylactic vaccines against HPV may lead to the misconception that development of therapeutic approaches are less important. On the contrary, due to heterogeneity of dysplasia-inducing HPV types, the high number of currently infected persons, possible breakthrough infection when prophylactic immunity wanes with time, and the need in developing countries that may not have access and financial resources to widespread prophylactic vaccination, there is a continued need for therapeutic vaccines. Ideally, HPV vaccines comprise both prophylactic and therapeutic activity to yield best protection. As pre-clinical studies continue to advance, there is prospect of therapeutic vaccination to treat existing lesions. Positive consequences may include less invasive and less disfiguring treatment and fewer recurrent or progressive lesions. Probably, this will reduce cost, may allow for changes in screening intervals, and for the first time offer a treatment for infection before lesion development. Most importantly it will offer a psychological relief for individuals carrying a HPV infection that to date can not be treated.

Future tasks will be to design adequately controlled clinical trials for the new emerging vaccination strategies, with sufficient patient numbers and avoiding end-stage patients in order to be able to identify immune correlates of protection. Until now, certainty has been obtained that HPV vaccination is safe, immunity can be induced, and efficacy – at least in early and premalignant disease – can be expected. If the progress made in other fields of immunology and genomics is incorporated progress in therapeutic HPV vaccines will be stimulated.

Also advances in basic immunology will help vaccines to overcome tumour-induced immunosuppression, a tolerogenic disease, and a target cell that has already evaded the immune system for years and escaped elimination. Just increasing the number of antigen-specific T cells alone will probably not be enough. Also T cell homing to tumour sites and effector functions need to be improved and the immunosuppressive tumour micrenvironment needs to be addressed together with induction of proper processing and presentation of tumour-antigens by the cancer cell itself. Potentially, this could be achieved by a combination of vaccination with application of immune adjuvants supporting the local immune responsiveness in the patients. If also immunotherapy is combined with current treatments and reduction in tumour burden results may be further improved and lead to a decline in cervical cancer incidence and recurrence.

**CONCLUSION**

After years of research focussing on the development and introduction of prophylactic HPV-vaccines, the pace and enthusiasm of investigating therapeutic vaccines has again increased. A number of different approaches are under development or already in clinical testing. Now, patients are recruited with early invasive and premalignant disease. Specific immune responses are regularly induced without significant toxicity. Therefore, a basis has been laid for successful and well designed clinical trials and development of therapeutic vaccines that may further reduce cancer burden or eliminate residual disease after standard therapy. Most of these studies are conducted with patients suffering form cervical cancers. But certainly, these developments in therapeutic HPV-vaccination are also important for other mucosal HPV-associated malignancies like certain SCCHN.

**SUMMARY**

**NOVINE U TERAPIJSKOJ VAKCINACIJI PROTIV HUMANOG PAPILOMA VIRUSA**

U prevenciji i terapiji premalignih i malignih displazija uzrokovanih humanim papiloma virusom zabeležen je značajan napredak primenom skrining programa i nedavnim uvodjenjem preventivne vakcinacije. Čini se da će u budućnosti imunoterapijski metodi dati značajan efekat u zaustavljanju širenja HPV - uzrokovanih karcinoma. Displastične epithelne leziije i karcinom anogenitalne i orofarinksne regije u direktnoj su vezu sa HPV. Upravo ova činjenica razlikuje karcinome cervixa i HPV- uzrokovani skvamozni karcinom glave i vrata od drugih malignoma. Ekspresija onkogena je uslov izolovanja i onkogena. Ovi antigeni su specifični za tumor, ali istovremeno i određeno polje za razvoj terapijskih vakcina. Korelacijom imunog i kliničkog odgovora provedene su brojne kliničke studije prvenstveno ispitujući efikasnost vakcine kod karcinoma cerviksena i njegovih rekurzora. Iako je zabeležen odgovor T celija klinički uspeh primena vakcina još nije zado-
Developments in therapeutic human papillomavirus vaccination

voljavajući. To možemo pripisati imunosupresiji, imunoselekciji ili imunoproliferaciji od strane tumorskih čelija. Ne bi trebalo zanemariti ni individualno specifične faktore koji uzrokuju neefikasnost autonomne odbrane od početne infekcije. Bez obzira na teškoće, uticaj na imunosupresiju i primena vakcina u ranim stadijumima bolesti baca ključni faktor u budućnosti. Cilj ovog rada je prikaz nedavnih dostignuća u primeni terapijskih vakcina i procena faktora koji utiču na njihovu efikasnost.

Ključne reči: human papiloma virus, imunoterapija, terapeutika vakcina, imunomodulacija, kliničko ispitivanje, karcinom cervikska, karcinom skvamousnih čelija glave i vrata

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