

Foreword

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The year 2006 was marked by an important event in cancer prevention: 30 years after Harald zur Hausen for the first time hypothesized that human papillomaviruses may be associated with the development of cervical cancer, a prophylactic vaccine against certain types of these viruses was launched to the market in Mexico, the US, Canada, Australia, and several European countries. Initially, the very rare malignant conversion of condylomata accuminata tempted zur Hausen to speculate that infectious genital warts and cervical cancer may have a similar infectious causes. These considerations were strongly supported by observations made by Alexander Meisels in Toronto who found that replicating HPV infections led to the formation of “koilocytes” that are found in condylomata but also in early cervical intraepithelial lesions (CIN 1), the early precursors of invasive cervical cancer. Shortly thereafter, the papillomavirus genotypes 6 and 11 were isolated from condylomata and were used as molecular probes to identify related viral genomes in cell lines and biopsies of cervical cancers. These experiments led to the successful detection of HPV 16 and 18 in the early 1980ies. Subsequent research revealed that oncogenic HPV genes are present in almost all cervical cancers, that the viral genes E6 and E7 are continuously expressed in all cancer cells, that these genes confer transforming activities once they are expressed in cultured human epithelial cells *in vitro* and, importantly, that the inhibition of the expression of these genes results in loss of the neoplastic growth of cervical cancer cells. Since then a tremendous amount of knowledge has been gathered by many scientists, including epidemiologists, pathologists, clinicians and public health physicians on the global distribution of oncogenic papillomaviruses and their disease causing role. It turned out that these virus-

es are abundant agents infecting the majority of all humans at least once in their lifetime. They use an elegant replication strategy that permits high level expression of viral genes and multiplication of the viral genome with capsid formation only in terminally differentiated epithelial cells at the very surface of the epithelium that are going to be exfoliated as cellular debris anyhow. Thus, they cause little or almost no damage within the infected tissues and replicate usually unrecognized by the host. Danger occurs only when after a rather prolonged period of latent infection some basal cells lose molecular control mechanisms that restrain the virus and usually prevent active expression of viral genes in the basal cells. Uncontrolled expression of the viral oncogenes may then induce chromosomal instability and initiate a dangerous cascade of events that drive the cells through a series of pre-neoplastic lesions into invasive cancer cells.

All this knowledge was combined to design a plan to defeat this cancer-causing virus: Empty viral capsids that resemble normal virus particles, but lacking their dangerous genetic information, have been produced and were injected subcutaneously to stimulate the immune system of vaccinees to produce neutralizing antibodies that prevent the entry of infectious virus particles in the basal cells at risk of being infected by oncogenic papillomaviruses. Initial animal experiments and later large worldwide clinical trials showed excellent protection of the vaccinated individuals in almost 100 % against infectious papillomavirus particles. Thus, the development of these vaccines crowns the 30 year long discovery of human papillomaviruses as cancer causing agents that are responsible for at least the second most frequent cancer in women world wide and thus represent after smoking the second most important carcinogen on earth.

Despite all this success a word of caution: we have not yet reached all the goals. Cervical cancer still is an

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important and costly issue and the prevention approach will only work if at least most women in the world will have access to these vaccines. To achieve this, we will certainly need a lot of time, effort and money. The worst thing to do now would be to neglect the very successful screening programs for cervical cancer that made cervical cancer the prime paradigm for successful cancer prevention strategies. About 60 years ago George Papanicolaou developed a simple cytological staining technique that allowed to identify preneoplastic cells in cytological specimens taken by a little swab, brush or broom from the uterine cervix. Because of its simplicity this method became the most wide spread diagnostic test in oncology and led to reduction of the incidence of cervical cancer by about 70%. The vaccine has to compete with this success and there clearly will be a time period in that we will not be willing to abandon the one or the other.

For the time being, vaccination and screening have to go hand in hand. It is clear that screening needs to be adapted to the new demands. There is a lot of room for improvement in cervical cancer screening and a lot of opportunities to render it more cost-effective. The introduction of costly vaccines together with a costly and ineffective screening program is surely not acceptable. In this issue we have addressed these problems from many points of view covering all timely issues of HPV-related disease, screening techniques, molecular biomarkers as well as therapeutic and prophylactic vaccination approaches.

Jenkins summarizes the various histo- und cytopathological features associated with acute and persistent HPV-infections and provides the reader with the essential knowledge to understand how HPV gene products alter shape and function of normal epithelial cells.

Bosch and de Sanjose present a current and extensive survey of HPV and cervical cancer epidemiology. Moscicki gives an overview of HPV infections, screening, triage, and treatment in adolescents that is highly relevant for vaccination programs, since adolescents represent the primary target population and HPV infection in young girls emerges as a new problem. Shah and Westra provide an up-to-date review of HPV associated disease in the aerodigestive tract, including the benign recurrent respiratory papi-

lomatosis as well as head and neck cancers. Nindl and colleagues have summarized biological and clinical data on the role of human papillomviruses in non-melanoma skin cancer. Palefsky contributes a comprehensive overview of HPV infections in men with respect to disease patterns observed in men, transmission of the virus to women and the related issues concerning the possible vaccination of women and men. Moving towards new approaches in screening, Meijer and colleagues present an extensive survey of different HPV detection methods including genotyping and mR-NA detection together with different possible scenarios of their application. Pagliusi contributes an important article on the international standardization of HPV testing.

Further articles address the emerging research on new biomarkers for cervical cancer screening that appear to help to overcome several of the important limitations of the current cancer early detection strategies. Doorbar extensively reviews molecular processes in transition from viral infection to the development of high grade disease and cervical cancer. A special focus is put on the changes of the viral life cycle with effects on cellular genes and proteins. Wentzensen and von Knebel Doeberitz summarize the current state of the most promising biomarkers that have been identified so far for revised cervical cancer screening and triage programs and potential clinical applications. The last two articles finally deal with the exciting topic of prophylactic and therapeutic vaccines. Müller and Gissmann contribute an exciting historical essay of the discovery of HPV and the highly interesting process of development of therapeutic and prophylactic vaccines. Kast and colleagues present an excellent and very timely survey on therapeutic vaccines against HPV and associated disease with a detailed description of the lessons learned from the limitations of previous vaccination trials and of novel promising approaches.

We like to express our sincere thanks to all colleagues and scientists who took the effort to contribute to this selection of papers and very much hope that this issue will be an informative source of valuable information particularly for the growing group of people joining the field now and decided to help for their part to defeat human papillomavirus infections and associated cancers.