27th INTERNATIONAL PAPILLOMAVIRUS CONFERENCE AND CLINICAL WORKSHOP

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Clinical Workshop and Main Conference

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Preclinical Workshop "Gynecologic Oncology"

BERLIN • GERMANY

Press Conference

HPV-Related Cancers: On the Way to Better Prevention, Safer Detection and Better Treatment Results

Friday, September 16, 2011, 11 – 12 a.m.

Charité Campus Mitte, Luisenstraße 64
Bettenhochhaus, Conference room A (ground floor)
10117 Berlin

Your speakers:

Prof. Dr. rer. nat. Lutz Gissmann,

German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ)
Heidelberg

HPV Vaccination is Effective

PD Dr. Andreas M. Kaufmann,

Gynecologic Tumor Immunology
Charité University Medicine, Berlin

Second-Generation HPV Vaccines

Prof. Dr. med. Achim Schneider M.P.H.,

Director of the Department of Gynecology of Charité University Medicine, Berlin
Campus Charité Mitte – Campus Benjamin Franklin, Berlin

Having Children and More Quality of Life After Cervical Cancer: New Treatment Methods

Presentation: *Dr. Stefanie Seltmann*
German Cancer Research Center

Press office:
German Cancer Research Center (DKFZ)

Dr. Stefanie Seltmann
s.seltmann@dkfz.de

Dr. Sibylle Kohlstädt
s.kohlstaedt@dkfz.de

pressehpv@dkfz.de

Phone: ++49 (0) 6221 42-2854

Press Release

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HPV-Related Cancers: On the Way to Better Prevention, Safer Detection and Better Treatment Results

Almost 2,000 scientists from 78 nations will be meeting from September 17th to 22nd, 2011, at the ICC Congress Center in Berlin to exchange the latest research findings about cancer-causing human papillomaviruses and diseases associated with these pathogens.

When, in 2008, Harald zur Hausen was awarded the Nobel Prize in Medicine, human papillomaviruses, or HPV for short, were temporarily in the public focus. Zur Hausen, a physician and scientist at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg, had been awarded this high distinction for his discovery that specific papillomaviruses cause cervical cancer. On the basis of his findings, it was possible to uncover the role of these pathogens in the development of cancer. This provided the basis for developing vaccines that protect against infection with oncogenic papillomaviruses and, thus, against cervical cancer.

“Many areas of HPV research are currently in a very exciting phase. First results provided by Australian colleagues show that the vaccine is effective,” says DKFZ’s Lutz Gissmann, who is one of the organizers of the Berlin conference. In 2007, Australia was among the first countries to establish a nationwide HPV vaccination program. First evaluations of this program have now provided evidence that the vaccination is effective not only under strictly defined clinical trial conditions, but also when applied to a broad population: In girls who were vaccinated at a young age and, thus, before they started having sexual contacts, the number of precancerous lesions declined by 60 percent. This trend is also confirmed by the significant decrease by 73 percent in the incidence of genital warts after vaccination with the quadrivalent vaccine Gardasil®.

These first data already invalidate those concerns which have been voiced by many concerning the effectiveness of the vaccines. They show that the immune system of girls at that age is very well capable of mounting a defense against infection. Moreover, the decrease in precancerous lesions shows that after “chasing away” the high-risk HPV types 16 and 18 by the vaccination, no other cancer-causing HPVs appear to have taken their place.

However, Andreas Kaufmann, a virologist of Berlin Charité, emphasized: “Several conference contributions show how currently available HPV vaccines can be further improved – regarding not only their spectrum of efficacy but also production methods and, thus, final prices.” HPV virologists from the U.S.A. are testing the L2 protein of HPV as a

vaccination antigen. An L2 vaccine can be produced in bacteria, which saves the high costs of cell culture production. Moreover, immunization with L2 would protect from a very broad spectrum of cancer-causing papillomaviruses.

Therapeutic vaccinations, i.e., immune therapies to cure existing precancers, are also already in the clinical trial stage. A research team headed by Cornelis Melief from Leiden University in the Netherlands is presenting a vaccine which consists of 13 different protein sections (peptides) of the HPV 16 oncoproteins E6 and E7. It has already proven successful for treating precancerous stages of vulvar carcinoma.

Even though HPV vaccination will spare many women the diagnosis of cervical cancer in the future, it is not possible to completely prevent this disease. Therefore, physicians continue to work towards better treatment methods for affected women. Twenty percent of cervical cancer cases occur between the ages of 15 and 39 years. Thus, cervical carcinoma is the gynecologic tumor which affects the youngest women. „This means that more and more women are confronted with the diagnosis of cervical cancer while they are still in their family planning phase," says Achim Schneider, head of the Department of Gynecology of Charité in Berlin. Tailored to the needs of such patients, Schneider and his co-workers have developed a fertility preserving surgical method in which part of the cervix is removed. However, a number of criteria have to be fulfilled for this surgical method to be an option. "The cancer must not be too advanced," says Schneider. "If these criteria are met, our patients wishing for a child achieve a pregnancy rate of more than 50 percent after this type of treatment."

The fact that maternal age is increasing also results in more cervical cancers being diagnosed during pregnancy. In such cases, Schneider and his colleagues use the lymph node status as a basis to determine whether it is justifiable to delay cancer treatment. "Thus we are able to continue nine out of ten pregnancies and in most cases we will perform a cesarean delivery after the 35th week of pregnancy."

For physicians attending the 27th International Papillomavirus Conference, the Preclinical Workshop on September 16th will offer a special service: The surgeons will transmit surgical procedures directly into the auditorium, where Achim Schneider will explain the crucial steps of the operations to the expert audience.

Prof. Dr. rer. nat. Lutz Gissmann
German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ)
Heidelberg

HPV Vaccination is Effective

When the German Standing Vaccination Commission (STIKO) issued an official vaccination recommendation for girls aged 12 through 17 in March 2007, this sparked a controversial discussion about cervical cancer vaccination. Critics have pointed out that the "only" protection that has been proven to date is against precancerous lesions of the uterine cervix. Indeed, following the recommendations of a WHO expert board, the placebo-controlled trials evaluating the clinical effectiveness of the HPV vaccines used high grade cervical dysplasias (CIN 2/3), not cases of cervical cancer, as their primary endpoint. Using cases of cervical cancer as an endpoint is considered unethical, because this would mean that women in the control group with precancerous lesions would not be treated and just remain under observation until cancer develops. Another clinical endpoint is the protection against persisting HPV infection caused by the HPV types contained in the vaccine.

More criticism was provoked by the fact that the approval study, FUTURE II, was conducted with young women aged 16 to 26, while vaccination is recommended for girls aged 12 to 17 – an age group whose immune response may differ from that of the adult study subjects, as critics have argued.

By now, the two HPV vaccines, Gardasil® and Cervarix®, have been included in the vaccination recommendations of 28 countries. The vaccines have worldwide approval in many countries, and donation-funded focused immunization programs are ongoing in at least 17 developing countries.

With its program started in April 2007, Australia was among the first countries to establish a national vaccination program with the quadrivalent vaccine Gardasil. Along with a permanent vaccination program for girls aged 12 to 13 years, two "catch up" immunization programs for girls aged between 13 and 17 years as well as for young women aged 18 to 26 years were offered between July 2007 and December 2009.

In Victoria, the second most populous state in Australia, a telephone survey conducted in 2009 among 18-26 year-old women determined that 74 percent of those questioned had received one dose, 69 percent had received two doses and 56 percent had received the complete 3-dose vaccination.

By now, the Victoria Cytology Service has made data available on the incidence of low grade and high grade cervical lesions in the first three years after the vaccination program started [1]. The data were evaluated, stratified in five age groups, and they show for the first time that under non-study conditions the HPV vaccine also protects from high grade cervical lesions, which have to be regarded as precancerous stages.

Shortly after the vaccination program was launched, the incidence of high grade lesions among girls and young women under age 18 already decreased by 60 %. As could be expected, immunization protection manifests itself most strongly in the youngest girls, who had actually been vaccinated before starting to have sexual contacts. In the group of young women between 18 and 20 years, no continuous significant decline in new infections was observed over the whole study period. However, a slight decline was found in the second half of the time period. A possible interpretation of this is that most of the young women who had already been infected cleared

the infection spontaneously. Only afterwards will the vaccination show its effect by protecting from new infections.

As expected, no effectiveness was observed in adult women aged 20 to 30 years: Most of these women were almost certainly already infected with an oncogenic HPV at the time of vaccination.

For mild cervical lesions, too, no decline in incidence was expected, because only a minor portion of these is associated with HPV types 16 and 18, which are the targets of the vaccine.

The data from Australia show for the first time that the HPV vaccine is not only effective under defined study conditions, but also if applied to a whole population. This interpretation is further confirmed by results of another study coming from Australia: After introduction of the vaccination, a decline of 59 percent in the incidence of genital warts was observed in young women. It is noteworthy that this study also found a decrease by 28 percent in genital warts in young heterosexual men (but not in homosexual men!). Thus, it is apparent that men also benefit from the vaccination of their female partners due to the herd immunity phenomenon.

The Australian study on the incidence of cervical lesions also proves that the immune system of the youngest girls aged 13 to 17 years, in particular, is very well capable of generating a protective immune response to the viruses. Moreover, these data are not compatible with another criticism that has often been expressed: There is a fear that after the high-risk HPV types 16 and 18 have been “driven away” by the vaccination, other cancer-causing HPVs might take their place and, thus, counteract a decrease in cancer cases. If this was true, then we would not observe a decline in high-grade lesions today.

Even today, considering the slow process of tumor development, it is at least ten years too early to provide evidence of a factual decline in cancer incidence. However, the results from Australia provide every reason to believe that the vaccination will hold its promise.

[1] Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Julia M L Brotherton, Masha Fridman, Cathryn L May, Genevieve Chappell, A Marion Saville, Dorota M Gertig, Lancet 2011; 377: 2085–92

[2] Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. Basil Donovan, Neil Franklin, Rebecca Guy, Andrew E Grulich, David G Regan, Hammad Ali, Handan Wand, Christopher K Fairley, The Lancet Infectious Diseases, Volume 11, Issue 1, Pages 39 - 44, January 2011

Since 1983, Professor Dr. Lutz Gissmann has been head of the Division of Genome Modifications and Carcinogenesis at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg. Prior to that, he pursued research at the Institute of Clinical Virology of the University of Erlangen-Nuremberg (1974-77) and at the Institute of Virology of Freiburg University (1977-83). From 1993 to 1996 he was Director of Research of the Department of Obstetrics and Gynecology of Loyola University Chicago Medical Center and head of the Viral Oncology Program at Loyola University Cancer Center. From 1998 to 1999 he was head of research at MediGene in Martinsried, Germany.

PD Dr. Andreas M. Kaufmann,
Gynecologic Tumor Immunology
Charité University Medicine, Berlin

Second-Generation HPV Vaccines

The two substances Gardasil® und Cervarix®, which have been available in Europe since 2006 and 2007, have been the first vaccines against human papillomaviruses ever to be available on the market. As with most vaccines against bacterial or viral pathogens, we can expect that the protection achieved by immunization will be enhanced in various respects with every new generation of vaccines being developed.

In view of the fact that about 18 HPV types are known to be cancer-causing today, it seems useful, first of all, to broaden the vaccine's spectrum of efficacy. Currently available vaccines provide protection against the two high-risk HPV types 16 and 18, which are responsible for about 70 percent of cervical cancer cases; Gardasil® additionally protects from infection with HPV6 and HPV11, the primary agents causing genital warts.

The approval trial PATRICIA has already shown that Cervarix® also protects against infections with HPV types that are not contained in the vaccine. This so-called cross-protection covers virus types 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, of which HPV31 and 45, in particular, have a high oncogenic potential. For Gardasil®, too, cross-protection with the phylogenetically related HPV type 31 has been known [1].

The pharmaceutical companies are currently further developing their vaccines to offer protection against a broader spectrum of pathogenic agents. Thus, Merck is already in the clinical trial stage of testing a nonavalent vaccine which, in addition to HPV6, 11, 16 and 18, also protects from types 31, 33, 45, 52 and 58. The new vaccine thus aims to prevent 87 percent of all cervical cancers and 90 percent of all genital warts.

Alternatively, there are research approaches which aim to use other vaccinating antigens to achieve protection against a broader spectrum of HPVs. All currently available vaccines consist of the major capsid protein of papillomaviruses, L1, which spontaneously assembles into what are called virus-like particles (VLPs). The natural HPV capsid additionally contains a smaller protein, L2. Neither natural infection nor immunization with VLPs consisting of L1and L2 elicit neutralizing antibodies against L2, while vaccinating with recombinant L2 or with L2 peptides does. The explanation for this contradictory behavior is that L2, which plays a key role in viral entry of the cell, is usually turned towards the interior and therefore not accessible. The only time it is "visible" and accessible for the immune system is during the very process of viral infection.

L2 has a favorable characteristic which has made it more interesting for vaccine developers. The protein has a very low antigenic variability – probably because this was not needed in the course of evolution or because the protein's function requires a high degree of structural conservation. Therefore, vaccinating with L2 not only induces neutralizing antibodies against the homologous HPV type but also against other HPV types including even papillomaviruses of other species.

Using an intelligent combination of various L2 proteins, scientists have been able to achieve antibodies against a very broad spectrum of HPV types [2]. In order to imitate the success concept of the VLP L1 vaccine, i.e. the densely organized packaging of the antigen in a virus-like structure, colleagues from the U.S.A. have developed a mixture of eight different L2

peptides displayed on virus-like particles of the PP7 bacteriophage [3]. Mice immunized with this construct were protected from infection with eight diverse HPV types.

Moreover, what would also be particularly desirable to have is a so-called therapeutic vaccine, i.e., an immune therapy to cure existing precancerous lesions. A research group headed by Cornelis Melief of Leiden University in the Netherlands is already conducting clinical trials to test a peptide vaccine against precancerous stages of vulvar carcinoma. The team has developed a peptide vaccine from 13 synthetic long sequence segments of the HPV16 oncoproteins E6 and E7. [4]. As opposed to other viral proteins such as the capsid building blocks, L1 and L2, the E6 and E7 proteins are generally produced by all cells in advanced precancerous stages and cancers, and these can then be attacked by the immune system.

In a trial with 20 patients, precancerous lesions completely regressed in five cases and symptoms improved in twelve women. It is interesting that the success of this immune therapy can be related to a strong T cell response (a particular type of white blood cells) to the vaccine. This is a major prerequisite for continuing to specifically enhance the vaccine.

This successful approach shows that it is basically possible to develop a therapeutic vaccine. This means that women who have not received prophylactic immunization against HPV in their early youth may also be protected from the dangerous late effects of an infection with cancer-causing HPVs.

[1] H M Hepburn, A M Kaufmann: Nobelpreis für die Impfung gegen Zervixkrebs. Aktuelle Daten- und Leitlinienlage. Internist 50 (2009), 617–626

[2] Vaccination with multimeric L2 fusion protein and L1 VLP or capsomeres to broaden protection against HPV infection. Subhashini Jagu, Kihyuck Kwak, Robert L. Garcea, Richard B.S. Roden, Vaccine 28 (2010) 4478–4486

[3] A Pan-HPV Vaccine Based on Bacteriophage PP7 VLPs Displaying Broadly Cross-Neutralizing Epitopes from the HPV Minor Capsid Protein, L2. Ebenezer Tumban, Julianne Peabody, David S. Peabody, Bryce Chackerian; PLoS ONE August 2011, Volume 6, Issue 8

[4] Success or failure of vaccination for HPV16-positive vulvar lesions correlates with kinetics and phenotype of induced T-cell responses Marij J. P. Welters, Gemma G. Kenter, Peggy J. de Vos van Steenwijk, Margriet J. G. Löwik, Dorien M. A. Berends-van der Meer, Farah Essahsah, Linda F. M. Stynenboscha Annelies P. G. Vloona, Tamara H. Ramwadhdoebed, Sytse J. Piersmad, Jeanette M. van der Hulst, A. Rob P. M. Valentijn, Lorraine M. Fathers, Jan W. Drijfhout, Kees L. M. C. Franken, Jaap Oostendorp, Gert Jan Fleuren, Cornelis J. M. Melief, and Sjoerd H. van der Burg PNAS, June 29, 2010, 107:11895–11899

Associate Professor (PD) Dr. Andreas Kaufmann is a biologist and earned his Ph.D. from the Institute of Immunology and Genetics at DKFZ Heidelberg. From 1994 to 1997 he pursued research at Loyola University Medical Center and at Loyola Cancer Center, Chicago, U.S.A., in gynecology and in the Viral Oncology Program. Since then, his major research focus has been the development and clinical testing of therapeutic vaccines against cervical cancer. From 1998 to 2006, he worked at the Department of Gynecology of Jena University, where he did his 'Habilitation'. Since 2006, he has been head of the research laboratory 'Gynecologic Tumor Immunology' at the Department of Gynecology of Charité University Medicine Berlin.

Prof. Dr. med. Achim Schneider M.P.H.,
Director of the Department of Gynecology of Charité University Medicine, Berlin
Campus Charité Mitte – Campus Benjamin Franklin, Berlin

Having Children and More Quality of Life After Cervical Cancer: New Treatment Methods

Despite early detection programs, 6,200 women develop cervical cancer in Germany each year and 1,700 die from it. About three thirds of affected women are under the age of 59 years; twenty percent of them are even aged between 15 and 39 years. Cervical cancer is thus the gynecologic tumor that affects the youngest women.

The average age of pregnant women has increased continuously over the past decades. Therefore, an increasing number of women who still want to have children are confronted with the diagnosis of cervical cancer.

In such cases, surgery to remove part of the cervix (abdominal radical trachelectomy) may be considered as an option to preserve fertility. In this procedure, about two thirds of the cervix and half of the parametrium (surrounding connective tissue) are removed [1].

Criteria for this procedure are:

- Tumor size < 2 cm
- Tumor-free lymph nodes
- Tumor resection within healthy tissue is possible
- No tumor invasion into blood vessels

Ideally, the method is combined with sentinel lymph node dissection, which is advantageous particularly for patients with small tumors [2].

The recurrence rate with this surgical method is 4 percent; the mortality rate is 1.6 percent. The pregnancy rate of patients who wish to have a child is 56 percent. Despite a high miscarriage rate, two thirds of these women deliver the child after pregnancy week 36. However, any pregnancy after trachelectomy must be considered a high-risk pregnancy.

Further studies will have to show whether less extensive surgery yields equal oncologic safety in the long term.

With maternal age increasing, it happens more frequently that women are diagnosed with cervical cancer during pregnancy. In such cases, too, the treatment decision depends primarily on the status of the lymph nodes. Involved lymph nodes are the most important parameter used for deciding whether a pregnancy can be continued despite cancer. To safely determine the lymph node status, it is necessary to perform a minimally-invasive procedure called laparoscopy, which can also be done during pregnancy without problems.

In a recent study [3], we have been able to prove that laparoscopic removal of lymph nodes is not associated with a higher complication rate. In addition, we have shown that if the lymph node status is negative, it is justifiable from an oncologic perspective to delay cancer treatment until the child can be delivered by cesarean section.

[1] Marnitz, A. Schneider Berlin, Aktuelle Therapiekonzepte bei Frauen mit Zervixkarzinom. best practice Onkologie 3/2011

[2] Multicenter Validation Study of the Sentinel Lymph Node Concept in Cervical Cancer Christopher Altgassen, Hermann Hertel, Antje Brandstädt, Christhardt Köhler, Matthias Dürst, and Achim Schneider Journal of Clinical Oncology, 20. Juni 2008

[3] Invasive cervical cancer during pregnancy: Laparoscopic nodal evaluation before oncologic treatment delay. Giovanni Favero, Vito Chiantera, Agnieszka Oleszczuk, Valerio Gallotta, Hermann Hertel, Joerg Herrmann, Simone Marnitz, Christhardt Köhler, Achim Schneider, Gynecologic Oncology 118 (2010) 123–127

Professor Dr. Achim Schneider has been duly qualified to practice medicine since 1975 and, from 1977, worked at Ulm University Women's Hospital where he qualified as a medical specialist. In 1987, he finished his 'Habilitation' in the discipline of gynecologic oncology. In 1988-89 he studied to earn a Master of Public Health at Johns Hopkins University in Baltimore, U.S.A. From 1991-92, he worked as a research fellow in gynecologic oncology at the University of Arizona, Tucson, U.S.A. In 1994, he was appointed as a senior (C4) professor at Friedrich Schiller University in Jena. In 2004, he moved to Berlin to take on a professorship of gynecology specializing on Gynecologic Oncology at Charité University Medicine Berlin. Since 2004, he has also been head of Charité Interdisciplinary Breast Center.
Achim Schneider's main areas of interest are gynecologic oncology, human papillomaviruses and gynecologic surgery.