I S—1

Seroreactivities to HPV-16 Virus Like Particles (VLPs) using ELISA in the Patients with Cervical Neoplasia

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The late structural proteins of HPV-16 have recently been shown to self-assemble into virus-like particles from baculovirus system when expressed in insect cells (Kirnbauer *et al., J. Virol.*, 1993). The ability to generate preparative amounts of HPV-16 L1-L2 VLP may have implications for the development of a serologic assay to detect anti-HPV-16 virion immune responses to conformational epitopes and for immunoprophylaxis against HPV-16 infection. We attempted to investigate serologic responses in the sera obtained from Korean women with cervical neoplasia by ELISA using HPV-16 VLPs. All cervical neoplastic tissues of experimental cases were amplified and hybridized for HPV types by PCR using L1 consensus primers and type-specific oligomer probes. Among women with cervical neoplasia, HPV-16 VLP was positive in 79% (19/24) of HPV-16 positive cases and 36% (5/14) of HPV-16 negative cases (infected with other HPV types or noninfected), while it was positive in 18% (3/17) of normal controls (cancer free individuals).

The detection rate of antibodies to the HPV-16 VLP appears to be higher in the patients with cervical neoplasia, especially in HPV-16 positive cases. The HPV-16 VLP ELISA may be useful adjunctive diagnostic assay for screening the present and past infection to HPV-16, although the statistical and clinical significance of this interpretation should wait for the analysis of more cases.

I S—2

Immunologic Diagnosis and Monitoring of Cervical Cancers using *In Vitro* Translated HPV Proteins

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E6 and E7 proteins, the transforming proteins of oncogenic HPVs, are known to be associated with the risk of cervical cancer. In radio-immunoprecipitation assay using *in vitro* transcripted and translated HPV-16 E6 and E7 proteins, the patients with HPV-16 associated invasive cervical cancer (group I) had a greater seroreactivity than most of other groups which included the patients with invasive cervical cancer who were infected with other types of HPV (group II), cervical cancer patients with non-detectable HPVs (group III), the patients with HPV-16 associated cervical intraepithelial neoplasia (group IV), and unaffected normal controls having non-cervical lesions (group V). The sera of the patients in group I, as comparing with the sera of most of other groups, were significantly reactive with at least one protein (66.7% vs 0.0-25%) and with two proteins (22.2% vs 0.0%). Antibodies for HPV-16 E6 and E7 proteins were only detected in the patients with invasive cancer.

The prevalence rates of E6 positive sera were 0% (0/9), 33% (11/33), 35% (7/20), 56% (5/9) and 50% (1/2), and the rates of E7 protein were 0% (0/9), 6% (2/33), 25% (5/20), 44% (4/9) and 50% (1/2) from CIN through clinical stage I, IIa, IIb to III, respectively. The positivities to E6 and E7 proteins in cervical cancers were significantly increased with advancing the clinical stage ($P < 0.05$ for E6 and $P < 0.001$ for E7).

To examine the change of antibody titres of HPV-16 E7 protein at the time of diagnosis, during the treatment and follow-up, we have tested serial serum samples from 14 patients of group I. The positive levels of E7 antibldy were decreased when the treatment was effective but in one patient showing recurrence or progression, positive seroreactivity was maintained. Antibodies to HPV-16 E6 and E7 proteins seem to be effective virus-specific and disease state-specific markers of HPV-16 associated cervical cancer.