

Monoclonal antibodies against human papillomavirus E7 oncoprotein for diagnosis of cervical neoplasia and cancer

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Abstract

Cervical cancer is the second most common cancer among women worldwide with half a million of new cases every year. Cervical cancer is caused by oncogenic human papillomaviruses (HPVs), with HPV16 and 18 being the most frequently detected types. Genital HPV infections are common in the general population although most infections are cleared before causing malignancy. However a small proportion of the infections evade the immune system, become persistent and may cause cervical lesions and even invasive disease. Being the causative agent for cervical malignancy, HPV is an obvious target for cervical cancer diagnosis and prevention. Current screening programs, primarily based on cervical cytology, produce millions of suspicious samples every year. Specific tools to identify high-grade disease in these samples are needed to increase specificity for malignancy and thereby reduce referral rates and overtreatment.

In the current study, monoclonal antibodies were raised against the E7 oncoprotein. E7 is an absolute prerequisite of malignant transformation and the protein is expressed at increasing levels during cancer development. E7 is therefore a suitable marker for HPV-induced malignancy. Antibodies specific for the E7 protein of oncogenic HPV types were selected using immunological methods such as ELISA, Western blot, Immunocytochemistry and flow cytometry. Phage display was used to identify antibody epitopes thereby predicting and verifying antibody specificity. Two of the antibodies, recognizing HPV16 and 18 E7 respectively, demonstrated strong staining of dysplastic cells in HPV-positive specimens in immunocytochemistry and may thus have the potential to be used in a clinical setting. Since the antibodies detect the protein in Liquid-based cytology, which normally leaves residual sample after standard cytology, E7 testing can easily be performed without recalling the patient for additional sampling.

Immunological detection of the E7 oncoprotein is an attractive alternative for triage of suspicious and borderline cytology to highlight and identify the often rare dysplastic cells present in a cell scrape. E7 detection can further reduce subjectivity and be performed with only standard equipment and thereby make HPV-testing available also in less developed regions.

Keywords: Human papillomavirus (HPV), Cervical cancer, Cervical neoplasia, E7 oncoprotein, Monoclonal antibodies, Cytology, Immunocytochemistry, Phage display

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av

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Fakultetsopponent

Professor **Joakim Dillner**

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Avhandlingen baseras på följande delarbeten:

- I. Maria Lidqvist, Olle Nilsson, Jan Holmgren, Christina Hall, Christian Fermér. **Phage display for site-specific immunization and characterization of high-risk human papillomavirus specific E7 monoclonal antibodies.** *Journal of Immunological Methods*, 337 (2008) 88-96.
- II. Maria Lidqvist, Olle Nilsson, Jan Holmgren, Sebastian Hölters, Eva Röijer, Matthias Dürst, Christian Fermér. **Detection of human papillomavirus oncoprotein E7 in liquid-based cytology.** *Journal of General Virology*, 93 (2012) 356-363.
- III. Michael Lebens, Susanne Källgård, Christian Fermer, Maria Lidqvist, Hubert Bernauer. **Generation of plasmid encoded protein-specific overlapping peptide libraries and the mapping of B cell epitopes in HPV E7 oncoprotein recognized by monoclonal antibodies and antibodies in the serum of immunized mice.** *Submitted manuscript.*
- IV. Maria Lidqvist, Olle Nilsson, Jan Holmgren, Matthias Dürst, Elin Andersson, Peter Horal, Christian Fermér. **Clinical feasibility study of anti-E7 MAb for detection of HPV-induced neoplasia and cancer in liquid-based cytology.** *Submitted manuscript.*

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