Oral Session VII

Hepadnavirus and Papillomavirus Infections

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Anti-viral Approaches to Inhibiting the Replication of Human Papillomavirus DNA

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Human papillomaviruses (HPV) of the 'low-risk' type are responsible for benign skin and genital warts, while the 'high-risk' HPV types are now accepted as being involved in cervical cancer. The study of HPVs has long been hampered by the difficulty in culturing the viruses due to their extreme tissue specificity. HPV infects basal keratinocytes, but viral gene expression and completion of the viral life-cycle are closely coupled to keratinocyte differentiation which does not occur in conventional cell culture. We have exploited recent developments in HPV molecular biology and virus propagation in order to develop an integrated strategy for the discovery of anti-viral compounds affecting viral DNA replication. The strategy involves four screens. (1) A high-throughput biochemical screen based on the HPV E1 protein. It has recently been reported that bovine papillomavirus (BPV) E1 is an ATPase which binds the origin of replication and cooperates with E2 in initiating DNA replication. We have expressed HPV6b E1 in *E.coli* and found the purified protein to have ATPase activity. Initial results using this enzyme in a biochemical screen will be presented. (2) A cellular assay of transient HPV DNA replication in cell culture. Although HPV DNA will not replicate when introduced into cell lines, it has been reported that the use of constitutive expression vectors to produce E1 and E2 makes cell lines permissive for DNA replication. We are currently developing this system into a drug screen. (3) 'Raft' cultures of differentiating keratinocytes permissive for viral replication are being used as models of virus-infected skin. (4) An animal model based on xenografting of either human wart tissue or HPV-infected cell lines on to immuno-compromised mice. We have been able to demonstrate virus replication in grafted tissue.