New Jersey State Commission on Cancer Research
LAY ABSTRACT OF RESEARCH PROJECT

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Project Title: **Human Papillomavirus 16: regulation of polyadenylation**

Description: **Human Papillomavirus 16, a causative agent of cervical carcinoma, has a unique poorly understood way of regulating its late gene expression that we wish to investigate which could lead to improved treatments for cervical carcinoma.**

It is estimated that about 400,000 new cases of cervical carcinoma occur worldwide every year, and it is the second leading cause of cancer-related deaths among women after breast cancer. Because of the lack of early diagnosis and treatment, underdeveloped countries are most affected by cervical cancer. Human papillomavirus (HPV) DNA is found in over 90% of cervical cancers, and epidemiologic and laboratory studies have shown a causative role for HPV in these cancers, especially HPV16. This proposal focuses on HPV16 because it is most common HPV strain found in cervical carcinomas. For HPV16 to replicate it must be able to express both its early and late genes which are found in the ~8000bp long viral genome. Much work has gone into understanding the transcriptional regulation of the HPV16 viral genes but relatively little into the regulation of polyadenylation of the HPV mRNAs. The importance of polyadenylation, which is central to this project, is discussed below.

In general terms, post-transcriptional regulation of the processing of pre-mRNA includes splicing (intron removal) and polyadenylation and is an important control point in gene expression in eukaryotes and their associated viruses including HPV. Changes in the position of the polyA tail, via alternative polyA site choice, controls the final sequence content and activity of mRNA and the lack of a polyA tail causes the mRNA to be degraded. Although the polyA tail is essential for gene expression, regulation of polyA sites (the position where the polyA tail is added), either by alternative polyA site choice or by an “on-off switch” of a single polyA site, was generally considered rare. Remarkably, it is now estimated that 30% of human genes are expressed, as mRNAs with different polyA sites underscoring the importance of this poorly understood regulatory mechanism.

The 3'UTR of the late genes of both HPV16 and bovine papillomavirus 1 (BPV1) contain a Negative Regulatory Element (NRE) that inhibits the expression of the late genes by inhibiting the activity of the late polyA site. We have previously demonstrated the mechanism for how the bovine NRE functions and in this grant application we propose to use our expertise to investigate how the HPV16 NRE functions. We have also established collaboration with a world expert on HPV16 biology who will aid us in studying the NRE's role in the viral life cycle. In summary, these studies will contribute to understanding HPV16 biology and could identify the determinants that change during human keratinocyte development that permit HPV16 late gene expression. Insights learned from this will guide future research on HPV16 replication and could lead to a better understanding and treatment of HPV-related disease.