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Study suggests first molecular target to halt spread of HPV

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Penn State College of Medicine researchers have discovered the first molecular therapy to target cancer-causing components and thereby destroy a bona fide human papillomavirus (HPV) infection.

"Our results suggest that targeting therapies to the RNA that encodes a specific pair of proteins in HPV may break a chain that, left unhindered, promotes cellular proliferation and, potentially, cervical cancer," said Gary Clawson, M.D., Ph.D., professor of pathology, and biochemistry and molecular biology, Penn State College of Medicine. "Until now, there have been no effective and specific molecular treatments reported for HPV infections or for related papillomavirus infections."

The study, titled "The Inhibition of papilloma progression by antisense oligonucleotides targeted to HPV11 E6/E7 RNA" was published July 1, 2004, in the online version of the journal Gene Therapy.

HPV is one of the most common causes of sexually-transmitted infection in the world. Types of HPV can cause fast-growing lesions such as genital and planter warts, and a number of HPV types are considered to be "high-risk" for development of cervical dysplasia, a known precursor to cervical cancer. According to the U.S. Department of Health and Human Services, 20 million Americans are already infected with HPV.

To survive and proliferate, HPV-infected cells require continued production of two proteins called E6 and E7, which are created according to the instructions of RNA, or ribonucleic acid, templates. Clawson and his team supposed that by destroying RNAs used for production of E6 and E7 proteins, the virus would no longer be able to trigger cellular proliferation.

"There are some unique characteristics of E6 and E7 which make them good targets, most importantly, their critical role in overcoming cell growth control pathways," said Clawson, who is also director of the Jake Gittlen Cancer Research Center at Penn State Milton S. Hershey Medical Center. "We targeted the production of E6 and E7 proteins with two different substances to see if they would halt growth of the HPV lesions."

Clawson's team first used library selection, a process by which sites on the surface of RNA are evaluated to see which are most accessible for binding. They identified sites on the E6 and E7 RNAs for HPV 11, which can cause genital warts, and HPV 16, a high-risk HPV associated with cervical dysplasia and cancer. Although known to be difficult targets, Clawson's library selection process identified effective sites on both HPV 16 and HPV 11.

They then targeted the sites identified on HPV 11 with ASO407 - antisense oligonucleotide 407 - and/or DNAzymes, both of which are small pieces of DNA - the body's genetic instructions - which can render RNA useless and prevent it from creating more proteins. The two substances were tested in an animal model, in which human foreskin was infected with HPV 11, and then grafted onto immunodeficient mice. Five of 11 grafts treated with ASO407 showed eradication of the virus. Of seven small papillomas treated with ASO407 four were negative for the virus.

"If this can be regarded as a cure rate, this rate is comparable or even superior to that achieved with a currently-available therapy, called imiquimod, and other therapies," Clawson said.

In larger papillomas, one of four treated with ASO407 was negative, suggesting that ASO407 may be most useful clinically for treatment of early HPV-associated lesions. DNAzymes were less effective than ASO407, showing therapeutic effects in only three of 10 samples. Their effects appeared to be limited to the upper levels of the lesion.

"Despite an increase in our understanding of the relationship between HPV and cancer, few advances have been made in the treatment of HPV-associated lesions," Clawson said. "In this study we managed to design and test reagents targeted to the RNA that encodes E6 and E7 proteins of HPV 11. This may lead to alternative treatments to suppress HPV lesion progression."

The team is currently working on a similar treatment for HPV 16, which is the most important high-risk HPV and is involved in cervical dysplasias and oral and cervical carcinoma. The treatment may reach clinical trials in one to two years.

In addition to Clawson, other investigators included: Weihua Pan, Diane Thiboutot, and Neil D. Christensen, Penn State College of Medicine, Penn State

Milton Hershey Medical Center. Funding for the study was provided by Biosan, Inc., and the National Institutes of Health.