Compounds Designed to Bind Conserved Regions of Human Papillomavirus (HPV) DNA Show Broad-Spectrum Activity against High-Risk Genotypes

James K. Bashkin, Terri G. Edwards, Kevin Koeller, Urszula Slomczynska, and Chris Fisher

Cervical infections by the “high risk” human papillomaviruses (HPVs), including HPV16 and 18, are usually not treated upon their discovery, but are flagged for later “follow-up.” Traditional approaches to antiviral design for HPV have failed for a variety of reasons including the lack of traditional antiviral targets. Therefore, novel antivirals designed to specifically reduce viral persistence are needed. A series of pyrrole-imidazole polyamides was optimized via medicinal chemistry based on an original lead compound designed against a sequence within the ori of HPV16. A set of improved polyamides was prepared, including compounds that potently reduced both HPV16 and HPV31 copy number (compared with vehicle-control) in cells maintaining these genomes as episomes. Keratinocytes maintaining either HPV16 or HPV31 episomes were treated with increasing concentrations of polyamide or vehicle-control for 48h in order to study dose response behavior. Loss of episomal DNA was measured by Q-PCR. Of the 46 polyamides tested, including 16 control polyamides not derived from our core lead structure, 12 gave pseudo-IC50s 200 nM against both genotypes, while 4 reduced HPV16 and HPV31 episomal DNA copy number to undetectable levels. Southern blot analysis confirmed these decreases. Broad-spectrum activity is likely achieved due to high conservation in A-T rich regions among high-risk HPV genotypes and the binding degeneracy of polyamides. Treatment of cells with a lead polyamide, followed by removal of compound and passage of cells, resulted in a moderate rebound of viral DNA that did not return to control levels after 6 additional days in culture. Extension of the polyamide treatment period resulted in a remarkably-effective delay and inhibition of episomal DNA rebound. These results illustrate that targeting of the HPV ori with polyamides has the potential for potent and long-lasting effects on HPV DNA load.