Chemical Control of HPV Episome DNA Levels in Keratinocytes

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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.