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Targeting the genome of high-risk HPVs with large hairpin polyamides: Promising novel antiviral agents

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Human Papillomavirus (HPV) is a small, closed-circular dsDNA virus that infects mucosal and cutaneous epithelial tissues. HPV infections remain a major health issue, as viral persistence with one of the 15 isolated oncogenic HPV types has been identified as a key factor in the development of cervical cancer and HPV16 is implicated in oral cancers. Despite the fact that type-specific prophylactic vaccines, as well as nonspecific cyto-destructive and topical immune-stimulant treatments are available, the latter two with limitations from toxicity and other side effects, there are no specific antiviral treatments against HPV. We have employed a rational design of hairpin pyrrole-imidazole Polyamides (PAs) to target the AT-rich genomes of high-risk (oncogenic) HPV16, 18 and 31. PAs are synthetic agents that recognize the minor-groove of dsDNA in a reportedly sequence-dependent manner and impart structural alterations on DNA. We have synthesized a library of PAs that potently decrease the viral load in monolayer keratinocytes and organotypic rafts without cytotoxicity. We report that N-terminal substitution with a Tetramethylguanidinium (TMG) group of closely related anti-HPV polyamides can lead to improvement in the IC50 and/or IC90 antiviral parameters against HPV16, 18 and 31. Using DNase I footprinting and affinity cleavage methods, we have determined the binding affinities and sequence specificities of several lead compounds to the long control regions of HPV16 and HPV18. Although the dissociation constants are similar and do not account for the differences in antiviral activities, we observe differences in the binding distribution between non-TMG and TMG-substituted polyamides along the DNA.

Biography

Carlos H Castaneda previously worked as a Formulation Scientist in the design and development of immediate and extended release formulations at Mallinckrodt Pharmaceuticals. In 2012, he started his Graduate studies and is a PhD student at the University of Missouri-St. Louis.

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