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DNA-binding polyamides designed against E1, E2 binding sites of HPV DNA show dramatic anti-HPV activity in cell and tissue culture

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Abstract

A series of polyamides based on pyrrole-imidazole polyamides was designed to interfere with viral protein-viral DNA interactions at the origin of replication of the high risk human papillomavirus types 16, 18 and 31. The specific sites targeted were the E1 and E2 protein binding sites on the viral genomes. The initial library showed hits in cell culture screens. Activity was assessed by qPCR determination of viral DNA 48 h after treatment in cell culture. Dose response curves were determined in all cases, with at least triplicate points. Active compounds were further elaborated and modified in a series of subsequent libraries, with initial optimization achieving many sub-100 nM IC50s and apparent IC50's as low as 36 nM. Since the three viral genomes are not degenerate for polyamide binding in the target regions, we were surprised to find that a significant number of compounds showed broad-spectrum anti-HPV activity against all three viral subtypes investigated (16, 18 and 31). Although the MWs are high, excellent activity cell culture activity is seen, in agreement with related studies. Two compounds are in preclinical development and have been scaled up to >6 g. More recently, we have discovered a new class of polyamides functionalized at the N-terminus which are active to IC50s of ca. 10 nM. Most recently, important clues to the mechanism of action have been discovered: HPV-infected cells treated with active compounds show activation of one branch of the DNA Damage Response Pathway, while uninfected cells show no such response.

Biography

James K. Bashkin completed his D. Phil. at the age of 24 years from the University of Oxford (U.K.) and postdoctoral studies from Harvard University. He is co-founder and director of chemistry at NanoVir LLC and Professor of Chemistry & Biochemistry at the University of Missouri-St. Louis. He has published more than 60 papers, has 11 issued U.S. patents, and serves as an editorial advisory board member of Chemical Reviews