

April 15-16, 2019  
Paris, FranceJames K Bashkin et al., Ann Clin Lab Res 2019, Volume:7  
DOI: 10.21767/2386-5180-C1-002

## POLYAMIDES AS MULTIFACETED MOLECULES FOR MEDICINAL CHEMISTRY: ANTIVIRAL AGENTS FOR DSDNA AND NEGATIVE STRAND RNA VIRUSES

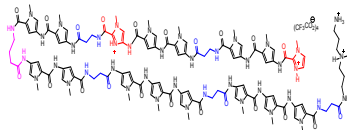
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**W**e discovered pyrrole-imidazole polyamides active against small double-stranded DNA tumour viruses (including human papillomavirus (HPV) types 16, 18, and 31 and polyomaviruses types SV40, BK-TU, and BK-Dun), and the negative strand RNA virus, vesicular stomatitis virus (VSV). The MWs of active polyamides range from high to low, and we observed active uptake of high-MW polyamides by human keratinocytes infected with HPV. For HPV, only large polyamides exhibited antiviral activity in cell and organotypic cultures. Recent results indicate that at least one small (inactive) polyamide is not taken up by infected keratinocytes. Active polyamides bind tightly and promiscuously to viral DNA according to quantitative DNase I footprinting, as measured by capillary electrophoresis. Recently, we coupled Next Generation Sequencing to hydroxyl radical footprinting in cellulose, providing direct evidence of drug binding to viral DNA inside infected cells. Efficacy of compounds does not correlate with binding affinity, though it loosely correlates with binding promiscuity. In the case of VSV, X-ray crystallography revealed a small, efficacious polyamide bound to both the viral negative strand RNA genome and the nucleocapsid proteins, and biophysical studies showed changes to the melting temperature of the nucleocapsid-like particle (NLP) in the presence of the active compound, which protected cells from virally induced lysis. Polyamides had been reported not to bind well to RNA. Our new result with VSV is a starting point for lead optimization.



### Biography

James K Bashkin has completed his DPhil from Oxford University and Postdoctoral studies from Harvard University's Department of Chemistry. He is Professor of Chemistry and Biochemistry at the University of Missouri-St. Louis and Co-Founder and Director of Chemistry at NanoVir LLC, an antiviral company. He also worked at Monsanto, Pharmacia, and Pfizer, has published more than 73 papers in reputed journals, and has served as an Editorial Board Member and/or Associate Editor of numerous journals, most notably as an Editorial Advisory Board member of Chemical Reviews from 1991-2014.

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