

DNA binding polyamides and the importance of DNA recognition in their use as gene-specific and antiviral agents

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Abstract

There is a long history for the bioorganic and biomedical use of N-methyl-pyrrole-derived polyamides (PAs) that are higher homologs of natural products such as distamycin A and netropsin. This work has been pursued by many groups, with the Dervan and Sugiyama groups responsible for many breakthroughs. We have studied PAs since about 1999, partly in industry and partly in academia. Early in this program, we reported methods to control cellular uptake of polyamides in cancer cell lines and other cells likely to have multidrug resistance efflux pumps induced. We went on to discover antiviral polyamides active against HPV31, where SAR showed that a binding size of about 10 bp of DNA was necessary for activity. Subsequently we discovered polyamides active against more-relevant forms HPV16 and 18, a subset of which showed broad spectrum activity against HPV16, 18 and 31. Aspects of our results are seemingly incompatible with reported DNA recognition rules. For example, molecules with the same cognate DNA recognition properties varied from active to inactive against HPV, and expected DNA target sequences differed dramatically for the three forms of HPV, yet broad spectrum antiviral activity was found for many PAs. We have since pursued the mechanism of action of antiviral polyamides, and polyamides in general, with collaborators at NanoVir, the University of Missouri-St. Louis, and Georgia State University. Dramatic consequences of β -alanine positioning and a lack of correlation between DNA binding strength (Kd) and biological activity (IC50) will be discussed.

Biography

Professor Bashkin completed his doctorate at age 24 from Oxford University (U.K.) and an NIH postdoctoral fellowship at Harvard University's Department of Chemistry. He is co-founder and Director of Chemistry at NanoVir, a Kalamazoo Michigan-based antiviral company. He has published more than peer-reviewed 60 papers, has 11 issued U.S. patents, shared a Presidential Green Chemistry Challenge award and Monsanto's Thomas & Hochwalt award, has served on American Chemical Society national award canvassing and selection committees, was associate editor of the Royal Society of Chemistry's Green Chemistry, and serves on the Editorial Advisory Board of Chemical Reviews.