

International Virology Conference

October 30-31, 2017 | Toronto, Canada

Noncytolytic destruction of dsDNA viral episomes: Anti-HPV agents for prevention of cervical and other cancers which modulate the DNA damage response and are also active against polyomaviruses

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Our program on anti-human papillomavirus (HPV) compounds was inspired by Dervan and Sugiyama's work with hairpin pyrrole-imidazole polyamides, but nothing we believed initially turned out to be true even though we discovered very active compounds. We initially targeted the long control region of the doubled-stranded, circular, negatively super-coiled DNA genome of HPV, hoping to block binding of viral proteins necessary for replication. We made large polyamides in an attempt to minimize their accessibility to human chromatin, and this size turned out to be important because activity was observed only for polyamides that bound at least one full turn of B-form DNA. However, it was immediately obvious that our active molecules were more powerful than theoretically possible for replication inhibitors. In fact, after further experimentation, we found that antiviral polyamides were causing active degradation of viral DNA. We were surprised to discover broad spectrum activity against HPV16, 18 and 31, all oncogenic strains, given the reported rules for polyamide-DNA recognition on which our structures were originally based.

More recently, we conducted preclinical safety studies on lead and backup compounds, discovered a new mechanism of action for polyamides and antivirals in which the DNA Damage Response is activated and found that our compounds fail to follow reported polyamide-DNA binding rules. We discovered various guanidinium N-termini that improved antiviral activity, and we embarked on massively parallel sequencing-based studies to further probe the mechanism of action. Antiviral results were also extended to other small DNA tumor viruses, the polyomaviruses SV40, BKV-Dun, and BKV-TU.

Speaker Biography

James K Bashkin completed his DPhil from Oxford University (UK) and Post-doctoral studies from Harvard University. He is the Professor of Chemistry and Biochemistry at the University of Missouri- St. Louis and is the Director of Chemistry at NanoVir, a company he co-founded. He has published more than 70 papers in reputed journals, 15 issued US patents, and served as an associate editor and Editorial Board Member for the Royal Society of Chemistry and American Chemical Society. He received the Thomas and Hochwalt Prize (1994), Presidential Green Chemistry Challenge Award (1998), and Roland Tibbetts Award (2006).

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