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## Artificial nucleosides and nucleotides: Applications as diagnostic and therapeutic agents against cancer

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**T**emozolomide is a DNA damaging agent that is a frontline therapeutic agent against brain tumors including glioblastoma (GBM). Unfortunately, resistance to temozolomide occurs frequently, thus limiting the overall utility of the agent. Resistance can be caused by a variety of different cellular defects. However, an emerging mechanism of resistance reflects the ability to DNA polymerases to misreplicate DNA lesions that are left unrepaired. In this study, we provide evidence that the therapeutic efficacy of temozolomide can be significantly increased by co-administration of an artificial nucleoside, denoted as 5-nitroindolyl-2'-deoxyriboside (5-NIdR), that efficiently and selectively inhibits the replication of DNA lesions generated by temozolomide. Conversion of 5-NIdR to the corresponding nucleoside triphosphate 5-NITP *in vivo* creates a potent inhibitor of several human DNA polymerases that can replicate damaged DNA. This inhibition accounts for the ability of 5-NIdR to synergize with temozolomide to increase apoptosis of tumor cells. In a murine xenograft model of GBM, treatment with temozolomide only delayed tumor growth while co-administering 5-NIdR with temozolomide caused complete tumor regression. Preliminary toxicology studies demonstrate that high doses of 5-NIdR do not produce the side effects typically observed with conventional nucleoside analogs such as fludarabine and gemcitabine. Collectively, these pre-clinical results demonstrate pharmacological proof of concept for the coordinate inhibition of translesion DNA synthesis as a strategy to improve chemotherapeutic responses in aggressive brain tumors.

### Biography

Dr Anthony Berdis is an Associate Professor in the Chemistry Department at Cleveland State University. He is also Co-Founder and Chief Scientific Officer for Red5 Pharmaceuticals, LLC which develops novel agents targeting drug-resistant cancers. Dr Berdis received his PhD in Biochemistry from the University of North Texas. He performed an NIH sponsored postdoctoral fellowship under the direction of Professor Stephen J Benkovic at the Pennsylvania State University. Dr Berdis has published over 80 research papers and book chapters. His research has been funded by the National Institutes of Health, the National Science Foundation, and the Department of Defense.

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