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# Inhibitors of DNA glycosylases as potential therapeutic drugs in cancer

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Ionizing radiation and most chemotherapeutic agents kill tumor cells by damaging DNA. The efficacy of DNA-damaging agents may be influenced by increased DNA repair capacity in tumors that results from overexpression of DNA repair proteins. Inhibition of activities of these proteins in tumors is a promising approach to enhance the efficacy of DNA damage-based therapy. Intense efforts are underway worldwide to find inhibitors of DNA repair proteins. Of these proteins, DNA glycosylases are involved in the first step of base excision repair mechanism by removing modified DNA bases. Despite the successes with other proteins of this repair pathway, the development of inhibitors has been lagging for DNA glycosylases. Recently, several DNA glycosylases including NEIL1, OGG1 and NTH1 were identified as potential targets in combination therapeutic strategies. We designed experiments to discover small molecule inhibitors of NEIL1 as the proof-of-principle glycosylase. A fluorescence-based assay was developed to detect both glycosylase and AP lyase activities of NEIL1.We screened small molecule libraries for inhibitors of NEIL1 activities. Several purine analogs were found, whose postulated presence in the active site of NEIL1 fits with the paradigm of NEIL1 action on damaged purines. We also applied gas chromatography/isotope-dilution tandem mass spectrometry to measure the effect of small molecule inhibitors on glycosylase activities of NEIL1, OGG1 and NTH1. The release of modified DNA bases known as substrates of these enzymes was measured in the presence and absence of the inhibitors. These data revealed that several of the purine analogs were general glycosylase inhibitors with one compound being the most effective inhibitor for all three enzymes. However, there were significance differences in inhibition of enzymatic activities among these DNA glycosylases. Overall, this work forms the foundation for the future discovery of DNA repair inhibitors as drugs in cancer therapy for the entire family of DNA glycosylases.

**Biography:**

Dr. Dizdaroglu has obtained his PhD at the Karlsruhe Technical University, Germany, and subsequently worked for seven years at the Max-Planck-Institute for Radiation Chemistry, Germany, before moving to US in 1978. He has been at the National Institute of Standards and Technology (NIST) for more 30 years. In 2006, Dr. Dizdaroglu was conferred upon the rank of NIST Fellow. He published more than highly cited 230 papers. Dr. Dizdaroglu received numerous scientific awards including the Hillebrand Prize of the American Chemical Society and the Gold Medal Award of the US Department of Commerce. He was also awarded two Honorary Doctorates.