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Transition State Analogue Containing Oligonucleotides as Inhibitors of Base Excision Repair Glycosylases

Abstract: A variety of endogenous and exogenous sources (including environmental toxins) can produce reactive oxygen and nitrogen species that are capable of damaging DNA. The low redox potential of guanine makes it particularly vulnerable to oxidation, a common product of which is 8-oxo-7,8-dihydroguanine (OG). Base excision repair (BER) enzymes have evolved to address this damage and restore genomic integrity, preventing diseases such as cancer. However, base lesions such as OG are also abundant in cancer cells, and in recent years, new therapies aim to inhibit the catalytic activity of DNA repair enzymes or to trap enzyme-DNA complexes. This is because BER enzymes (such as MUTYH and hOGG1) can repair DNA lesions, thereby reducing the cytotoxic effects of anticancer drugs and contributing to the survival and metastasis of cancer cells. As such, the goal of my research is to develop high affinity nucleic-acid based inhibitors of BER glycosylases that will be useful structural and chemical biology tools. A significant portion of this work will be aimed at determining necessary features of a successful nucleic acid-based inhibitor to enter cells. This will include understanding how to effectively transfect the probes in live cancer cells, as well as utilizing X-ray crystallography to guide the design of potent and highly specific inhibitors of BER glycosylases. Ultimately, we hope that this may provide a unique strategy to target and inhibit specific BER glycosylases in cancer cells.