“DNA Glycosylases: Novel Targets for Small Molecule-induced Synthetic Lethality”

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Many nonsurgical cancer treatments utilize combinations of chemotherapeutic agents and targeted ionizing radiation that can produce severe toxic side effects for patients. This proposal focuses on the development of a novel treatment strategy that has the potential to increase therapeutic effectiveness, while potentially reducing adverse side effects. The underlying principle is the recent discovery of a previously unidentified therapeutic target, the DNA base excision repair (BER) DNA glycosylase NEIL1 and the potential therapeutic benefit of the inhibition of this enzyme. NEIL1 functions in the BER pathway to catalyze the excision of DNA bases that have been damaged by ionizing radiation or other sources of reactive oxygen. The potential to exploit NEIL1 as a potential therapeutic target has been recently demonstrated in studies showing that synergistic cytotoxicity was achieved by the depletion of NEIL1 and treatment with drugs that function to limit DNA replication through dNTP pool depletion, such as 5-fluorouracil (5-FU) and methotrexate (MTX). These drugs are routinely used in combination with ionizing radiation for the treatment of patients with a variety of solid tumors. We hypothesize that effective inhibition of this glycosylase has the potential to be used in a variety of therapeutic settings thereby increasing the therapeutic index of the combined treatments. The investigative team that has been assembled for this application brings diverse complementary expertise, including structural biology, biochemistry, cell biology, radiation biology, animal model systems, immunology, and human clinical perspectives.