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Topic Category: 4121-ASIP Drug discovery for cancer treatment

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First Author is a: Graduate Student
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First Author Degree: MS, MPH, MA. Med, or equivalent

Presentation Preference: Indifferent

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Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society
Keywords: 1. Cancer Drug Discovery 2. GBM 3. Resistance-MGMT
Awards: ASIP Trainee Travel Award, ASIP Promoting Diversity in Science Trainee Travel Award, HCS-Sponsored Trainee Travel Award

Structure-based drug design to overcome temozolomide resistance in glioblastoma (GBM) through a dual inhibition of MGMT and base excision repair

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The incidence of pediatric and adult brain tumors has continued to rise and temozolomide (TMZ) has remained the sole choice for chemotherapy in these cancers. TMZ alkylates the DNA to generate N7-methylguanine (~70%) and O6-methylguanine (~6-9%) lesions, with the latter being considered the cytotoxic residue. However, the N7-methylations can also contribute to cell killing by producing abasic sites, strand-breaks, and mutagenicity. Therefore, inhibiting the two major mechanisms of resistance to TMZ in brain cancers, namely, the MGMT DNA repair which removes the O6-methyl groups and the APE1 endonuclease, which cleaves the apurinic/apyrimidinic sites is a logical choice for enhancing the alkylator therapy; incidentally, both these proteins are highly expressed in brain tumors. Pseudosubstrates for MGMT such as O6-BG + TMZ therapies suffer from a high level of bone marrow suppression and there is no clinically approved inhibitor for APE1. Recently, we discovered that nitroaspirin (NCX-4016) is a powerful and clinically relevant inhibitor of human MGMT for increasing the efficacy of alkylating agents (Proc of AACR 54, p1094, 2013). Further extensive structure-activity relationship studies revealed that the 3-hydroxybenzyl nitrate moiety of NCX-4016 is essential for its MGMT inhibition activity. To develop a dual inhibitor of APE1 and MGMT, we designed a hybrid compound called MGAP-9 by combining 3-hydroxybenzyl nitrate with 7-Nitroindole-2-carboxylic acid, a known potent, nontoxic, and cell-permeable APE1 inhibitor through an ester bond. MGAP-9 exhibited significant inhibition of MGMT activity and a corresponding decrease in protein levels in both concentrations- and time-dependent manner. Similarly, we observed potent inhibition of APE1 nuclease activity both in vitro and in tumor cells using a biotin-labeled oligonucleotide/polyacrylamide gel-electrophoresis assay. Inhibition of both targets occurred at pharmacologically achievable concentrations (5-25 μM). MGAP-9 exhibited more than 100-fold sensitization of various GBM cell lines towards the methylating agents such as TMZ and Dacarbazine, but surprisingly not to BCNU or CCNU. A substantial increase in γ-H2AX further confirmed the DNA damage induced by MGAP-9 through a dual inhibition. In addition, the hybrid drug displayed potent anti-angiogenic activity against human umbilical vein cells (HUVECs). Finally, MGAP-9 showed significant regression of tumor growth in mouse orthotopic glioblastoma xenograft models and did not elicit systemic toxicity at the therapeutic doses used. The findings suggest the clinical relevance of MGAP-9 and its usefulness in reducing the TMZ doses to curtail the marrow suppression in brain tumor therapy