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Exploring New Chemotherapeutic Strategies Against Brain Cancer

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Exploring New Chemotherapeutic Strategies Against Brain Cancer

College of Science and Health Professions

Departments of Chemistry and Biology

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Abstract

Approximately 4,000 children in the United States are diagnosed each year with a brain tumor. Brain cancers are the deadliest of all pediatric cancers as they have survival rates of less than 20%. Typical treatments include surgery and radiation therapy. However, chemotherapy is the primary therapeutic option for children, especially against aggressive brain tumors. An important chemotherapeutic agent is temozolomide, an alkylating agent that causes cell death by damaging DNA. In this project, we tested the ability of non-natural nucleosides developed in our lab in order to increase the ability of temozolomide to kill brain cancer cells. Our results show that combining low doses of our nucleoside with temozolomide kills more cells compared to treatment with either compound individually. The increase in efficacy is specific for temozolomide as similar effects are not observed in cells treated with other chemotherapeutic agents such as cisplatin, 5-fluorouracil, and taxol. High-field microscopy techniques demonstrate that the combination of our nucleoside and temozolomide causes cell death via apoptosis as opposed to necrosis. A model is provided describing how our novel nucleoside analog increases the cell-killing effects of temozolomide by inhibiting the misreplication of damaged DNA created by this agent. Collectively, these studies provide pharmacological evidence for a new treatment strategy to more effectively treat patients with brain cancers.