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Pharmacological and Pre-Clinical Testing of 5-NIdR as a New Therapeutic Agent Against Brain Cancer

College of Sciences and Health Professions

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Abstract

Approximately 4,000 children in the United States are diagnosed annually with a brain tumor. Brain cancers are the deadliest of all pediatric cancers as they have survival rates of less than 20%. Although surgery and radiation therapy are widely used to treat adult patients, chemotherapy is the primary therapeutic option for children. One important chemotherapeutic agent is temozolomide, an alkylating agent that causes cell death by damaging DNA. In this project, we tested the ability of a specific non-natural nucleoside developed in our lab, designated 5-NIdR, to increase the efficacy of temozolomide against brain cancer. Cell-based studies demonstrate that the combination of 5-NIdR and temozolomide kills more cells compared to treatment with either temozolomide or 5-NIdR used alone. Microscopy techniques demonstrate that the combination of 5-NIdR and temozolomide causes cell death via apoptosis rather than necrosis. Animal studies using xenograft (nude) mice were performed to evaluate the *in vivo* efficacy and safety of this drug combination against brain cancer. Preliminary results are provided which indicate that treatment with 5-NIdR does not inhibit the rate of tumor growth. In contrast, treatment with temozolomide reduces the rate of tumor growth but does not lead to the complete elimination of the tumor. Striking results are obtained using 5-NIdR and temozolomide together as this drug combination causes a significant reduction in tumor size. Finally, mice treated with the combination of 5-NIdR and temozolomide do not show overt signs of side effects such as weight loss, dehydration, or fatigue. Collectively, these studies provide pharmacological evidence for combining 5-NIdR and temozolomide as a new treatment strategy to effectively treat brain cancers.

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