TMZ+X: siRNA-based Synthetic Lethal Screening and Synergism with TMZ as a Novel Approach to Inhibition of Proliferation in GBM

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Glioblastoma multiforme (GBM), the most common type of primary brain tumor, is universally fatal with median survival ranging from 9–16 months. Although a significant effort has been focused on the development of conventional therapeutics, few treatments prolong survival. In the context of combination therapies, employing newer targeted drugs together with broad-spectrum cytotoxic drugs remains a compelling approach to treatment. A rational approach to identifying the molecular targets in tumors that confer synergy to a specific cytotoxic drug will facilitate the development of combination therapies. RNA interference is a powerful tool for the identification of components of cellular signaling pathways. Combining a siRNA library with standard care may aid the discovery of targets, whose inactivation would enhance synthetic lethality. Temozolomide (TMZ), a standard of care for GBM, was used as an exploratory drug to identify synthetic targets using siRNA against the DNA repair genes in glioma stem cells (GSC). Genomic DNA was isolated, barcoded siRNA representation in each cell line was compared to the control cells, and computational tools were used to identify and prioritize candidate genes by statistical significance. Further investigation showed silencing of only BRCA1 potentiated TMZ-induced cytotoxicity as measured by cell viability assay, protein expression, and cell apoptosis. In conclusion, the findings in this study highlight BRCA1 as a potential target for enhancing the efficacy of TMZ, prompting the innovation of a novel combination therapy using pyridostatin (PDS) to successfully induce BRCA1 downregulation via G-quadruplex stabilization and the development of the G.L.I.O nanoparticle delivery system.

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