

A Novel Efflux Pump Inhibitor Improves Chemotherapeutic Efficacy Against P-glycoprotein-expressing Glioblastoma Stem Cells

Kodali, Sravan (School: Christian Brothers Academy)

Lustig, Samuel (School: Christian Brothers Academy)

The most commonly administered chemotherapeutic agent in Glioblastoma (GBM) treatment, Temozolomide (TMZ), fails to generate a clinically significant response in over 50% of patients due to Multidrug-Resistance (MDR). ATP-binding cassette (ABC) transporters comprise a fundamental mechanism of MDR within chemoresistant GBM. Inhibition of two ABC transporters, P-glycoprotein (P-gp/ABCB1/MDR1) and the breast cancer resistance protein (BCRP/ABCG2/CDw338), was hypothesized to improve TMZ efficacy. Ko143, an analog of a mycotoxin, has recently been shown to display inhibitory activity over both transporters at high concentrations ($>1\mu\text{M}$). Here, we present a combinatorial treatment composed of TMZ and Ko143 to target chemoresistant GBM stem cells (GSCs). The effects of the treatment on two patient-derived GSC lines, GBM9 and GBM146, were investigated. At IC₅₀ values, GBM9 exhibited 5.3-fold greater TMZ sensitivity relative to GBM146, characterizing GBM9 as a negative control ($p<0.0001$). Additionally, GBM146 showed 43.66-fold overexpression of P-gp relative to GBM9 ($p<0.01$), indicating that P-gp likely contributes to MDR within the GSC lines. Cell viability was analyzed using assays that quantify cellular oxidative metabolism (ATP-Glo assay, MTS assay). Results showcased lower TMZ IC₅₀ values for GBM146 stem cells treated with TMZ+Ko143 compared to TMZ alone, for a 41.07% increase in chemotherapeutic efficacy ($p<0.01$). Further, flow cytometric assessment proved Ko143 alone does not promote apoptosis or necrosis and has a nonsignificant effect on GBM146 cell cycle. Promising results of Ko143 and TMZ combination therapy have demonstrated possible implications of P-gp and BCRP inhibition via Ko143 as a novel method to enhance TMZ efficacy within chemoresistant GBM patients.

Awards Won:

