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**Exploring alternative anti-glioblastoma candidate**

Glioblastomas are a type of brain tumor originating in astrocytes. There are limited treatments for glioblastoma and the available treatments leave patients with poor quality of life and does not increase survival. The main obstacle for developing new and more effective glioblastoma therapies is inability of anticancer drugs to penetrate the Blood Brain Barrier (BBB). The current standard of care for a patient diagnosed with glioblastoma consists of surgical resection, radiotherapy, and chemotherapy with Temozolomide. Tumor cells treated with temozolomide eventually become resistant and patients are often left with poor quality of life. Fenofibrate is a drug originally used to treat high cholesterol but was previously shown to kill glioblastoma cells *in vitro*; however, fenofibrate does not cross the blood brain barrier. Our lab has previously described the design and testing of chemically modified metabolic variants of fenofibrate based on its chemical structure benzylphenoxy-acetamide (BPA). The physicochemical properties predict its increased ability to penetrate the blood brain barrier and were calculated using the following algorithms: Central Nervous System Multiparameter Optimization algorithm (CNS-MPO) and the BBB_Score. This work aims to describe the metabolic activity and cytoxicity of one of the compounds, PP21. The glioblastoma IC50 for PP21, tested in LN229 human glioblastoma cell line and in patient-derived GBM12 isolates, was over 20-fold (1.5 μM) lower in comparison to FF. The observed cytotoxicity involved a severe and immediate blockade of mitochondrial respiration followed by increased glycolysis, which in low glucose environment (1g/L), triggered a severe drop of intracellular ATP, activation of AMPK-induced autophagy, and ultimately necrosis-like glioblastoma cell death. However, addition of glucose attenuated PP21-induced glioblastoma cytotoxicity. Therefore, we tested a new approach to challenge glucose-dependence of the PP21 treatment, which involves addition of specific glycolysis inhibitors: Gnetin H (GH – resveratrol trimer), and lonidamine (LND). Our cell culture data show that both PP21+GH, and to a lesser extent PP21+LND, were both cytotoxic to glioblastoma cells and helped eliminating glioblastoma cells in a high glucose environment. Although PP21/GH drug combination seemed to be more effective, we were not able to deliver GH effectively into the brain tumor tissue, therefore, we selected PP21+ LND drug combination for the future efficacy testing in the intracranial xenograft glioblastoma model. Importantly, our data show that PP21 can penetrated both artificial BBB model membranes and, importantly we have detected PP21 in the brain tissue at clinically relevant concentrations following intraperitoneal drug delivery.