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**“Anti-glioblastoma Effects of Glucose-Independent
Benzoylphenoxyacetamide (BPA) Variants”**

Glioblastomas are notorious for being the most aggressive, lethal, and challenging to treat brain tumors. Current therapies against glioblastoma include surgical resection, followed by a combination of radiotherapy and concurrent treatment with temozolomide (TMZ) for maintenance. Unfortunately, these standard therapies often yield suboptimal results, leading to an average survival time between 12 and 18 months for patients. The limited availability of therapeutic options renders glioblastoma a formidable disease. We have previously documented the potent anti-glioblastoma properties of several synthetic metabolic compounds. These compounds were derived from the chemical structure of widely used lipid-lowering drug, fenofibrate, and possess a general molecular framework known as benzoylphenoxyacetamide (BPA). These compounds were shown to abruptly halt mitochondrial respiration, and effectively induce apoptosis in low glucose environments. However, extensive in-vitro and in-vivo analyses of these same BPA compounds show that their anti-glioblastoma effects are attenuated in the presence of glucose. Based on our findings, we put forth two independent approaches that can potentially counteract glucose-dependent treatment. Firstly, we propose the utilization of a novel drug candidate, PP12, which shares a phenol moiety similar to the active ingredient in Tylenol (acetaminophen). Secondly, we suggest employing glycolytic inhibitors alongside our compounds that have previously shown to inhibit mitochondrial respiration. Both approaches were tested in this study with the objective of selecting a new glucose-independent BPA variant or a set of synergic compounds for subsequent in-vivo and anti-glioblastoma testing. Dozens of compounds were assessed using computational analysis of the following parameters: solubility (logS), blood–brain partitioning (logBB), and probability of entering the CNS calculated by the Blood Brain Barrier Score (BBB Score) and Central Nervous System—Multiparameter Optimization (MPO-CNS) algorithm. Out of an initial pool of 300 BPA variants, three compounds were further evaluated for anti-glioblastoma activity in vitro during this study. In cell culture, all three compounds exhibit cell toxicity toward glioblastoma cells. Among them, PP12 and PP211 displayed a substantial increase in cytotoxicity under normal glucose (4.5g/L) conditions. Moving forward, PP12 will be tested in tandem with several glycolytic inhibitors such as: 2-deoxyglucose (2-DG) and Gnetin H (GH). Research findings indicate that sequential administration of glycolytic inhibitors followed by our newly developed PP compounds enhances cytotoxicity, even in normal glucose environments. In contrast, simultaneous administration of these agents has only mild-additive effects. The hypothesized mechanism behind this heightened cytotoxicity is as follows: pretreatment with 2-DG or GH leads to the inhibition of glycolysis, which in turn triggers a compensatory rise in mitochondrial respiration. Subsequently, the introduction of our PP compound disrupts the functionality of cancer cells' mitochondria, ultimately resulting in cell death.

