New Generation Drug Development Pipeline From in silico Identification to Preclinical Evaluation for Novel Drug Candidates in Glioblastoma

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Glioblastoma(GBM) is the most common malignancy of the central nervous system in adults. Despite medical advancements, the continued shortfall of many treatments such as Temozolomide, alongside the stagnant survival rate improvements (<13%) have led to pressing concerns for novel drug discovery methodologies. This study developed and utilized two key stages within the drug discovery process: drug-target prediction and in-vitro preclinical functional evaluation to identify a safe, bioactive, and effective treatment for GBM. Preliminary analysis on mechanisms of cell proliferation were conducted on GBM in order to identify a target. Stage 1 fabricated a novel five phase in-silico pipeline for drug-target prediction against Ephrin-Type-A Receptor 2. 1562 FDA approved drugs were run against the developed pipeline and analyzed for bond type, location, repulsion, Gibbs free energy, stability, interactions over time, blood brain barrier permeability, and possible false positives (PAINS). These results provided five plausible hits: Empagliflozin, Mycophenolate mofetil, Canagliflozin, Rivaroxaban, and Carvedilol. Stage 2 involved the preclinical evaluation of the top five predicted drug candidates using an in-vitro Suphorhodamine-B cytotoxicity assay on glioblastoma cell lines U251 and SF295. Canaglifozin and Empagliflozin exhibited promising results with IC50 values around 40 μM. Mycophenolate mofetil (IC50: 5μM) and Carvedilol (IC50:16μM) showcased highly promising results, a major improvement from serendipity approaches. Mycophenolate mofetil and Carvedilol results warranted further testing in pancreatic cell line SUIT-2 due to similar mechanisms of cancer progression. SUIT-2 results paralleled effectiveness noticed in GBM affirming testing within clinical trials.