Targeted Combination Treatment for Glioblastoma Multiforme (GBM) Using Polymeric Nanoparticle

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Glioblastoma Multiforme (GBM) is an aggressive cancer that originates from astrocytes and spreads to spinal cord and other parts of the brain. Increase in replication of glial cells leads to advantageous mutations in the tumor. In 2015 about 15,320 deaths were reported due to GBM. Five-year survival is less than 5% making GBM a dreadful cancer. Current treatment involves complex invasive surgery, followed by chemotherapy and radiation. There is a desperate unmet need for a targeted treatment of GBM with minimum damage to the surrounding normal tissue. Combination treatments are increasingly being used to target multiple hallmarks of cancer. The goal of this study is to develop a combination therapy to treat GBM using Poly (lactic-co-glycolic acid) (PLGA) nanoparticles encapsulated with three different drugs namely gefitinib, temozolomide (TMZ) and GSK461364 each with a unique target. Nanoparticles facilitate combination of multiple drugs for simultaneous delivery to cancer cells in a single nano-sized platform. Gefitinib is a Tyrosine Kinase inhibitor, which competes for ATP-binding site of EGFR-TK. TMZ methylates DNA of tumor cells, resulting in apoptosis. GSK461364 is a Polo-like Kinase (PLK-1) inhibitor that blocks the G2/M transition in tumor cell cycle. These three distinct hydrophobic drugs are tested on U-87 MG (human malignant glioma) and MDA-MB-231 (triple negative breast cancer) cell lines. PLGA is attached to Polyethylene glycol (PEG), which is conjugated to transferrin receptor (TfR) binding peptide for targeting TfR overexpression, common in GBM. PEG is known to increase the circulation half-life *in vivo* and improves colloidal stability of nanoparticles. These transferrin peptides bind to TfR (or CD71) and enable the entry of PLGA across Blood Brain Barrier (BBB). Results of characterization, *in vitro* drug release profiles, stability at 37°C and 4°C, cytotoxicity assay, electron micrographs of nanoparticles containing drugs and fluorescent imaging will be presented.

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