PROJECT DESCRIPTION

Each year about 7 out of 100,000 people are diagnosed with *malignant* glioma, also classified by the World Health Organization (WHO) as Grade III and IV gliomas. Grade IV is also referred to as glioblastoma multiforme (GBM). Hallmark characteristics of GBM include uncontrolled cell proliferation, diffuse infiltration, and resistance to apoptosis. These features, at least in part, account for GBM's poor prognosis and resistance towards radio- and chemotherapy, and a median survival of just 12-15 months even with the most aggressive treatment. Identifying and testing new drugs and innovative therapeutic approaches for GBM are therefore critically needed. One promising radiosensitizer in early testing is the second-generation ATM inhibitor (ATMi), KU-60019. Our submitted work (Biddlestone-Thorpe et al) currently under review and revision demonstrates for the first time in an animal glioma model that KU-60019 is a highly effective radiosensitizer of p53 mutant GBM but not genetically matched p53 wild-type. Camptothecin (CPT) is an extensively studied topoisomerase I inhibitor that primarily kills tumor cells during DNA replication. Therefore, we hypothesize that a 'synthetically lethal' drug combination that possesses CPT and the predecessor ATMi will act synergistically and kill p53 mutant glioma more effectively while sparing the brain. To make it eventually a clinically acceptable modality, Dr. Hu Yang and Dr. Kristoffer Valerie have been collaborating during the past few years to develop a dual-drug platform consisting of a novel clickable polymer vehicle for CPT delivery (provisional patent filed) and poly(lactic-co-glycolic acid) (PLGA) nanoparticles for ATMi delivery. The drug combination platform is meant to be deposited once by intra-tumoral convection-enhanced delivery (CED) to provide sustained, local release of CPT and ATMi over several weeks to enhance therapeutic effect and avoid systemic toxicity. This research is interdisciplinary in nature, requiring expertise in nanotechnology and drug delivery, and brain tumor biology and imaging. Dr. Yang and Dr. Valerie have the necessary complementary expertise essential for the success of this research. We have made significant progress on the research with prototype nanoconjugates already in testing, several studies already published and one joint-publication. Since there is no direct funding support for this research, it is critical to obtain a follow-on grant to expand this exciting and innovative approach. Our goal is to secure an NIH MPI R01 award for this highly innovative new therapeutic approach. In fact, as a first attempt we submitted an application 6/5/2012. Unfortunately, the grant was not funded but will be resubmitted. The reviewers thought *"the MPI team is highly qualified in their respective areas of expertise. The innovation lies in the approach and the drugs used"* and identified some weaknesses including the lack of optimal formulation and doses that should be determined for the application. Thus, the objective of this Massey Cancer Center (MCC) multi-PI research project is to address critiques received on our previous MPI R01 submission by improving our preliminary data to successfully compete for an NIH award. The overarching **Aim** of this proposal is to characterize and optimize a modular, dual-drug delivery platform with a defined time window for sustained release and synergetic drug activities and demonstrate proof-of-principle antitumor effects in an animal model. A novel, 'synthetically lethal' drug combination based on a CPT-polymer co-delivered with ATMi PLGA surfactant-coated nanoparticles will be formulated, tested, and optimized. We will demonstrate the tunability of the delivery system and achieve sustained release and synergistic drug activities over a 2-week window. The synthesis and formulations will be characterized and evaluated analytically and biologically to verify formulation stability, drug release kinetics, and tumor-specificity in vitro. Tumor penetration using near-infrared imaging tracers and target validation by immuno-histochemistry repair foci assay will determine drug spread as well as stability of nanoconjugates in vivo. We will use GBM orthotopic xenograft models to test, validate, and optimize our novel strategy with focus on extending the survival of mice. Optimal formulation of polymer-nanoparticles will be injected intra-cranially by convection-enhanced delivery (CED) to achieve high local presence and slow, protracted drug release. The effect of p53 in the response to these drugs will be determined.