Dual PI3K/Akt Inhibition: A New Strategy to Improve Drug Delivery in Glioblastoma Therapy

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Background: Glioblastoma multiforme (GBM) is a devastating brain cancer with limited treatment options. Surgery and radiation increase patient survival, but cannot completely remove the tumor and remnant cancer cells regenerate into even larger and more aggressive tumors. Therefore, chemotherapy is required for GBM post-surgery treatment. However, treatment of brain tumors with chemotherapeutics has been largely ineffective due to the drug efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) at the blood-brain and blood-tumor barriers where they restrict anti-cancer drugs from entering the brain and tumor tissues. Thus, P-gp and BCRP render chemotherapy ineffective, which is a critical clinical obstacle.

Hypothesis: We hypothesize that dual PI3K/Akt inhibition will reduce P-gp- and BCRP-mediated efflux transport activity by downregulating transporter expression at the blood-brain barrier.

Methods: We used Confocal Microscopy to measure P-gp and BCRP transport activity in isolated brain capillaries. Transporter protein expression was measured with Western blotting. We established an intracranial U87-luc2 GBM mouse model and tracked tumor growth with both MRI and in vivo bioluminescence imaging. Survival was analyzed with a Kaplan-Meier plot.

Results: Our in vivo data show that combination treatment with LY294002 (PI3K inhibitor) and triciribine (Akt inhibitor) decreases P-gp and BCRP protein expression and efflux transport activity. Dose and time course experiments show that the strongest effects were obtained 24 hours after injecting mice with a single dose of a 25 mg/kg LY294002 and 1 mg/kg triciribine combination. These data suggest that decreasing blood-brain barrier P-gp- and BCRP-mediated efflux through PI3K/Akt inhibition could be a new strategy to increase brain uptake of chemotherapeutic drugs. To test this approach, we established an intracranial U87-luc2 glioblastoma mouse model. Our preliminary data obtained by IVIS and MR imaging and Kaplan-Meier analysis show that with increasing size of the implanted tumors the health of the mice declines, and that average survival after tumor implantation is 31 days.

Conclusions: We will use the U87-luc2 glioblastoma mouse model to assess if dual PI3K/Akt inhibition to reduce P-gp/BCRP-mediate efflux transport will improve brain uptake of chemotherapeutic drugs. We will test the hypothesis that this increase in brain uptake of anticancer drugs reduces tumor size and increases survival of primary GBM bearing mice.