DETERMINATION OF TUMOR RESPONSE TO HYPOXIA-ACTIVATED PRODRUG TH-302 IN RAT GLIOMA MODELS

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Target Audience: Researchers and clinicians interested in utilizing functional diffusion maps for treatment studies.

Purpose: Functional diffusion mapping (fDM) has the potential to be an early biomarker of chemotherapy efficacy by spatially monitoring treatment-induced changes in the apparent diffusion coefficient (ADC)[1]. While chemotherapy is generally cytotoxic to all cells, tumor hypoxia is associated with chemotherapeutic resistance, which has led to the development of hypoxia-activated cytotoxic prodrugs, such as TH-302[2] (Threshold Pharmaceuticals Inc.). As tumor hypoxia is spatially heterogeneous, the treatment response will likely vary spatially in tumors, and thus an imaging approach to monitor treatment response would be clinically advantageous. In this study, we determined tumor response to TH-302 in two rat glioma models expected to have differential responses based on differences in their tumor hypoxic burden. In addition to MR-based tumor volumes, diffusion-weighted images were acquired pre- and post-treatment to monitor dynamic changes in diffusion in treated and untreated rats.

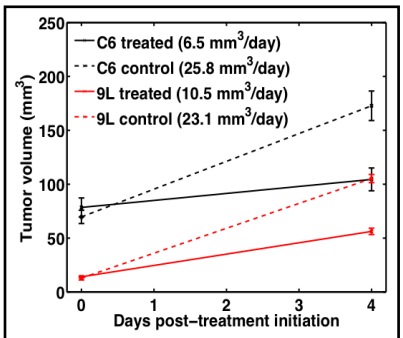

Figure 1: Mean tumor volumes for treated and control C6 and 9L rats. Mean growth rates in parentheses.

Methods: To study TH-302 treatment response, C6 glioblastoma and 9L gliosarcoma rat tumor models were utilized to provide a range of tumor hypoxia (C6 are relatively hypoxic, 9L are more normoxic).[3] MRI (4.7T, Agilent) was performed at pre- and post-treatment time points to obtain tumor volumes and diffusion-weighted images. Following pre-treatment imaging, treatment with TH-302 (50 mg/kg, treated group C6 n=8 and 9L n=6) or sterile saline (control group C6 n=8 and 9L n=6) was performed for 4 days. Post-treatment imaging was performed 1 day after the final treatment (4 days after pre-treatment). Diffusion-weighted images were acquired with a fast spin echo sequence (TR = 2s, TE = 28ms) with two b-values (200 and 800 s/mm^2) in 3 orthogonal directions. Following image registration between time points, fDM maps were computed from ADC pre- and post-treatment using a threshold of 0.4 x 10^{-3} mm^2/s.[1]

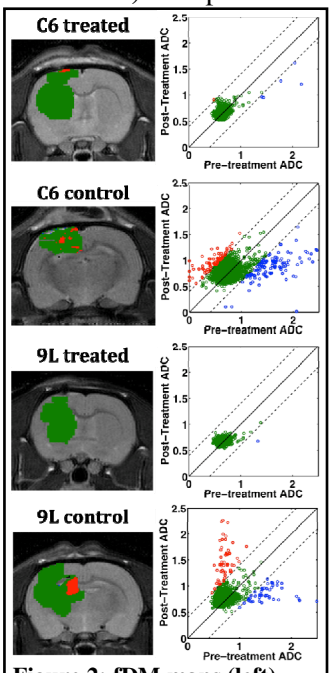

Figure 2: fDM maps (left) and scatter plots (right) in treated and control C6 and 9L tumors.

Results: Figure 1 shows the pre- and post-treatment tumor volumes for treated and control C6 and 9L rats. The mean growth rates for the C6 and 9L tumors were significantly different between untreated (25.6 and 23.1 mm^3/day, respectively) and treated (6.5 and 10.5 mm^3/day, respectively) animals ($p<0.05$). Figure 2 shows example fDM maps and scatter plots for treated and control C6 and 9L tumors. Treated animals showed a narrower range of post-treatment ADC values compared to control rats.

Discussion: Treatment with TH-302 resulted in a five-fold and two-fold decreases in the tumor growth rates of C6 and 9L tumors, respectively. These findings are consistent with previous reports that the C6 model exhibits more hypoxia than the 9L model, which is characterized by mild to moderate hypoxia. Work is ongoing to understand the underlying mechanisms of the observed dynamic ADC changes with and without treatment, as they possibly reflect a complex combination of treatment-induced cell death, necrosis, and new tumor growth. Histology in a subset of these animals is currently underway.

Conclusions: TH-302 is a promising hypoxia-activated drug and was shown to have a significant effect on tumor growth rates in two glioma tumor models. TH-302 is expected to selectively affect hypoxic tumor regions – which likely varies spatially and may result in either localized cell death or a decrease in growth rate, highlighting the need for spatially sensitive measures of cellular changes that could be indicative of response to hypoxia activated drugs such as TH-302.

References: 1. Moffat BA, et al. Neoplasia (2006) 8(4):259. 2. Liu Q, et al. Cancer Chemother Pharmacol (2012) 69(6):1487. 3. Khan N, et al. International Journal of Radiation Oncology*Biology*Physics (2009) 73(3):878.