# Effects of Targeted Nanoparticle-Based Antiangiogenic Therapy on Brain Tumor Metabolism and Progression - MicroPET and MRI Study on a Rat Glioblastoma Model

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## Introduction

Glioblastoma is a primary brain tumor with poor prognosis and low survival rate. The purpose of this study is to monitor metabolic changes during tumor progression with or without anti-angiogenic treatment in a rat glioma model. This novel nanoparticle (NP)-based anti-angiogenic approach is a non-viral gene delivery system using $\alpha_v\beta_3$ to target tumor vasculature. A mutated raf gene is delivered to cause apoptosis in tumor endothelium. PET imaging with radio-tracer $^{18}$F-FDG has been widely used in clinical practice to monitor glucose metabolism; while T2-weighted MRI provide high quality brain tumor anatomy. Combination of these two imaging modalities on the time course along tumor growth allows one to monitor the effect of our therapeutic NP on tumor progression.

## Materials and Methods

Fisher rats were divided into 3 groups. Treated (Group 1, n=10) and control groups (Groups 2, n=8) received RT2 tumor cells implanted intracranially into the striatum. Normal group (Group 3, n=5) received no tumor cells or treatment. Group 1 received an $\alpha_v\beta_3$ targeted NP that carried a mutated Raf gene (NP-ATP$^{\mu}$-Raf) complex. This gene disrupts the VEGF and FGF mediated signaling pathway. Group 2 received saline. Three treatments with targeted NP (Group 1) or saline (Group 2) were conducted starting day 6 after tumor implantation. Animals in both groups were imaged with $^{18}$F-FDG PET to monitor glucose uptake, and with T2-weighted MR sequences to record tumor on the days they received treatments and two time points after the treatments were finished. Animals in the control and normal groups were imaged on microPET and MR at the same dates when the treated animals were imaged.

## Results

Figure 1 summarizes the results of the Treated group. An increased FDG uptake in brain early in the treatment period followed by a constant decrease of PET signal in the tumor area starting day 10 after tumor implantation and lasted until the end of the study (6 months). In MR tumors showed reduction in tumor size after the treatment period. Figure 2 summarizes the results of the Control group. Animals had an increasing FDG uptake in PET and an increasing tumor volume in MR over the course of the study. Animals with no tumor had normal PET and MRI images (data not shown). All the control animals died between 15 to 27 days post tumor implantation.

## Conclusion

MR images showed that the NP slowed tumor progression with subsequent encephalomalacia, while PET images showed that this agent caused an initial increase then a significant decrease in metabolic activity in brain tumors. We hypothesize that two factors may be involved in the increasing PET signal in the beginning of the treatment: (1) vessel normalization prior to vascular apoptosis and (2) hypoxia and subsequent vessel apoptosis caused by the destruction in vasculature caused by NP therapy. Signal drop on both PET and MR toward to the end of study indicates destruction of the tumor mass. We conclude that MRI and PET imaging combined can be powerful to monitor tumor progression and to follow therapy.

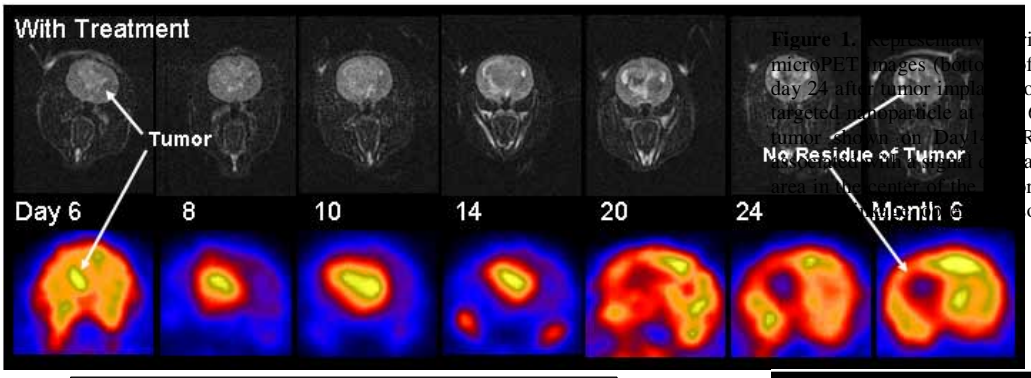


**Figure 1.** Representative serial T-2 weighted MR (top) and $^{18}$F-FDG microPET images (bottom) of Group 1 (treated) animals from day 6 to day 24 after tumor implantation. Treatments were conducted using $\alpha_v\beta_3$-targeted nanoparticle at 6, 8, and 10. Brightness on the rim of the tumor shown on Day14 MR indicates the development of necrosis area in the center of the tumor. Decrease in the corresponding PET images. Dark area in the center of the tumor on Days 20 and 24 MR images represent no tumor to in the corresponding PET images.

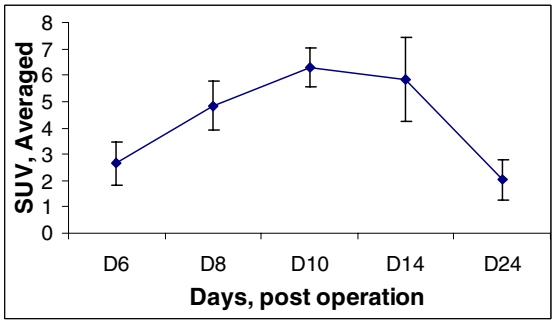


**Table 1.** Standard Uptake Value (SUV) of 18F-FDG in rat brain tumor with treatment of $\alpha_v\beta_3$ targeted nanoparticles (Group 1). SUV increases up to day 10 followed by a continuous decrease till the end of the study.

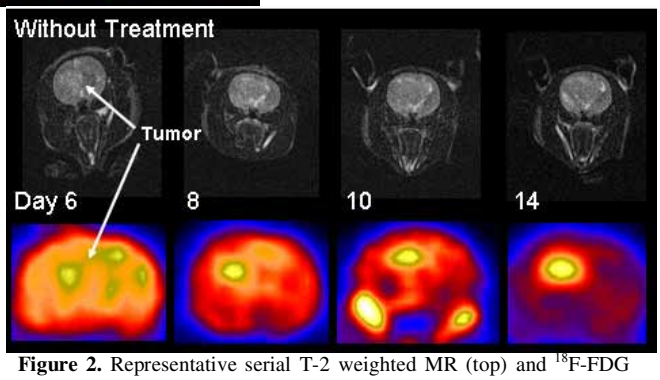


**Figure 2.** Representative serial T-2 weighted MR (top) and $^{18}$F-FDG microPET images (bottom) of Group 2 (untreated) animals from day 6 to day 14 after tumor implantation. Signal intensity and tumor volumes remain increasing till the end of time course when the animal died.