

#### Purpose:

Molecular targeted therapies affecting tumor and vasculature are currently used as anti-cancer strategies. However, their effect on the tumor-vasculature system is currently poorly understood and quantified. We developed an imaging-based computational model to simulate tumor and vasculature development, and investigated the effects of Sunitinib, an anti-angiogenic receptor tyrosine kinase inhibitor, *in silico*.

#### Methods:

PET scans of tumor hypoxia ( $[^{61}\text{Cu}]\text{Cu-ATSM}$ ) and proliferation ( $[^{18}\text{F}]\text{FLT}$ ) were taken as model input. The hypoxia scan reflecting tumor oxygenation (pO<sub>2</sub>) was used to simulate initial tumor vasculature. Vessel growth rate and tumor cell division probability were hypoxia dependent. The proliferation scan determined the tumor cell division rate. Vascular regression was Sunitinib dependent and tumor cell death hypoxia dependent. Tumor volume and oxygenation were temporally evaluated for drug dosage of 0, 10 and 40 mg/kg/day and therapy discontinuation.

#### Results:

Dose dependent changes in tumor pO<sub>2</sub> and volume could be observed by day 2 and 5 respectively, indicating a 3 day lag between micro-environmental and physical characteristic changes. As compared to an untreated tumor, 40 mg/kg/day dosage was twice as effective in decreasing tumor pO<sub>2</sub> as compared to 10 mg/kg/day dosage. Discontinuation of therapy on day 5 lead to increase in the tumor pO<sub>2</sub>, with both regimen pO<sub>2</sub> tending to the pO<sub>2</sub> of an untreated tumor. The rebound rate of pO<sub>2</sub> for the 40 mg/kg/day regimen was four times that of the 10 mg/kg/day dosage.

#### Conclusions:

Discontinuation of more aggressive therapy leads to a faster rebound of tumor pO<sub>2</sub> due to increased vessel recruitment rate which eventually increases in tumor volume. The model being a part of a more comprehensive tumor-vascular model will be useful for providing insight into the effects of therapy on the tumor-vasculature system. Incorporation of patient specific parameters enables the model to be used as a potential tool for tailoring therapy in future.