AbstractID: 13509 Title: Development of a computational model for quantifying vascular response to TKI therapy

Purpose: Tyrosine kinase inhibitors (TKIs) which target tumor vasculature have emerged as potential anti-cancer drugs. However their effect on the vasculature and tumor oxygenation status currently lacks proper quantification. We developed a computational model to analyze and quantify changes in vasculature and tumor oxygenation in response to TKI therapy.

Method and Materials: A three dimensional capillary structure was simulated and capillaries were classified as either mature or immature. Two effects of the TKI drug were simulated: vessel maturation and vessel regression. The initial proportion of mature vessels and vessel maturation fraction during therapy and were user-defined model parameters. Dose dependent vessel regression was simulated based on preclinical experimental data regarding the TKI drug sunitinib. The tissue oxygen tension (pO_2) from the modified vasculature was calculated and analyzed as a function of drug concentration, maturation fraction and initial state of vascular maturity.

Results: Tumor hypoxia was observed to increase with increased drug dosage up to a dose of 50 mg/kg/day. Further increase in dose did not affect the mean tumor oxygen tension significantly. As a model parameter, vessel maturation fraction was most effective in increasing the tissue pO_2 when the status of the initial vasculature was highly immature. Varying vessel maturation fraction (0 – 100%) resulted in a sevenfold increase in the mean tissue pO_2 when the initial vasculature maturity was set to 10% as compared to a twofold increase when the initial maturity was set to 50%.

Conclusion: The model suggests that TKIs have a more significant effect on vasculature when the initial vessel structure is highly immature. This model presents a key step in the development of a comprehensive vasculature model which can be used to tumor vasculature interactions during TKI therapy, and provide insight into the effects of therapy on the tumor vasculature system.