Evaluation of tumor oxygenation in response to an indole-based vascular disrupting agent using ^{19}F MRI

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Purpose: Vascular disrupting agents (VDAs) have been proposed as an effective broad spectrum approach to cancer therapy, but certain previous agents have proven sub-optimal. As such there is active development of novel agents designed to provide greater efficacy. OXi8007, an indole-based analog inspired by combretastatin A-4, was recently reported to show rapid acute selective shutdown of tumor vasculature, while leaving normal surrounding tissue intact, based on Color Doppler Ultrasound [1]. This would be expected to cause tumor hypoxia, a vital parameter if the drug were to be used in combination with radiotherapy. We have now explored the onset of hypoxia by using FREDOM (Fluorocarbon Relaxometry using Echo Planar Imaging for Dynamic Oxygen Mapping [2]) to assess the dynamic pO_2 changes following the administration of Oxi8007 at two different doses using an orthotopic breast cancer mouse model.

Methods: MDA-MB-231/luc cells ($1x10^6$) were implanted surgically into the mammary fat pad of five SCID mice. Three weeks later, MRI was performed at 4.7T. Mice were anesthetized (isoflurane/air) and hexafluorobenzene injected directly into the tumors ensuring distribution into multiple locations, as recommended [2]. Quantitative oximetry was obtained using ^{19}F MRI based on spin lattice relaxation of hexafluorobenzene (HFB) reporter molecule. Pulse burst saturation recovery echo planar imaging (EPI) was used to measure the spin-lattice relaxation rate, R_1, of HFB by arraying 14 delay times with a total acquisition time of 6.5 mins per map. Three pO_2 measurements were obtained for baseline air, and four with oxygen breathing challenge. Oxi8007 was administered IP *in situ* (full dose, 350mg/kg for four mice and half dose 180mg/kg for one mouse) and eighteen more pO_2 measurements were obtained over 2 hours followed by three to five measurements with air breathing.

Results and Discussion: Stable baseline pO_2 (mean 34.9±20.8 Torr, n=5, ranging from mean of 6 to 52 Torr) was observed when mice breathed air, with significant increase accompanying oxygen challenge (mean pO_2=159.0±77.6 Torr, n=5). Following VDA, the pO_2 decreased exponentially and stabilized around the pO_2 value originally observed with air breathing (full dose: pO_2=36.7±18.5 Torr, n=4 and half dose group pO_2=40.6 Torr, n=1). The rate of pO_2 decline averaged 0.042±0.021/minute for the full dose group and was slower (0.019/minute) for the half dose mouse. Further decrease of pO_2 was observed upon return to air breathing (pO_2=14.4±13.6 Torr, full dose group, n=4). The voxel-by-voxel pO_2 map revealed heterogeneous response to hyperoxic gas breathing challenge and VDA.

Conclusions: FREDOM revealed progressive hypoxiation in response to OXi8007 for both dose groups with a slower rate accompanying the lower dose. pO_2 maps indicated intra-tumor heterogeneity both with respect to oxygen breathing challenge and in response to the novel VDA (Oxi8007), though ultimately all tumor regions became hypoxic.

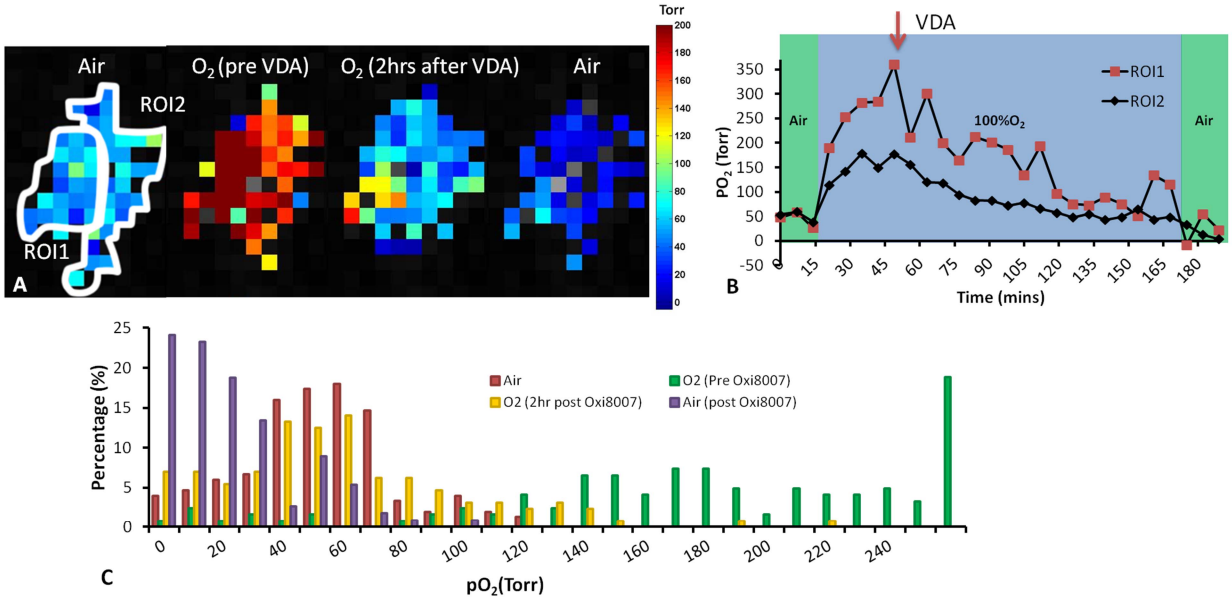

Figure. A. pO_2 maps of representative tumor with respect to O_2-challenge and full dose OXi8007. Two ROIs were identified as more and less responsive and the respective mean values are shown in B. C. Histogram showing pO_2 distributions with respect to O2 challenge and in response to OXi8007

References: [1] Hadimani, *et al. J Nat Prod.* 2013; 76:1668; [2] Zhao, *et al. Methods Enzymol.* 2004; 386:378

Supported in part by R01 CA140674