

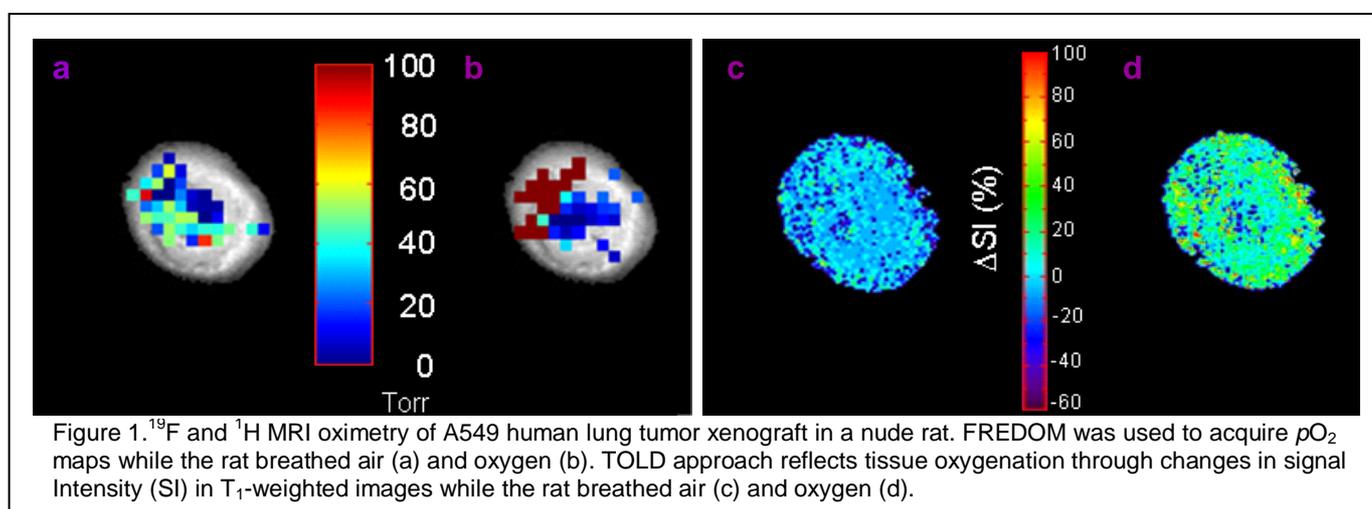
## Evaluation of lung tumor oxygenation using FREDOM and TOLD

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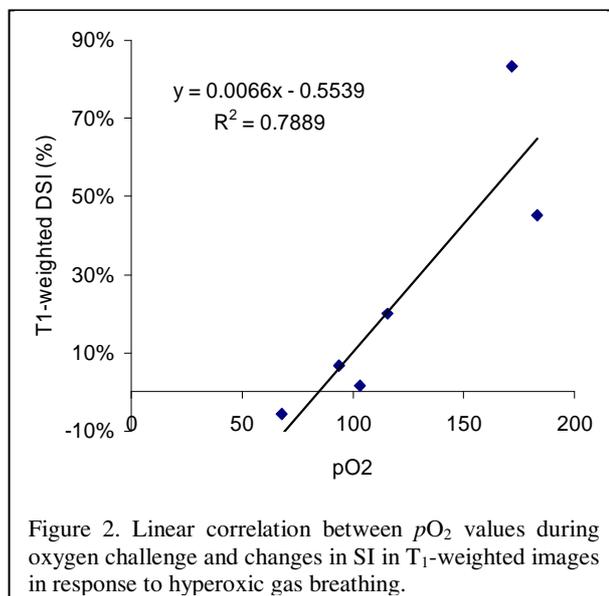
**Introduction:** Tumor oxygenation plays an important role in malignant progression, metastasis and response to various therapies. <sup>19</sup>F MR oximetry based on the reporter molecule hexafluorobenzene (HFB) using the FREDOM (Fluorocarbon Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping) approach offers quantitative measurements of  $pO_2$  with spatial and temporal resolution allowing the dynamic evaluation of response to interventions (1). Blood Oxygenation Level Dependent (BOLD) MRI based on  $T_2^*$  contrast induced by [deoxyhemoglobin], is sensitive to tumor vascular oxygenation and blood flow. Recently, studies have suggested a possibility of assessing tissue oxygenation based on the shortening of the tissue water  $T_1$  due to oxygen. This new approach has been named Tissue Oxygenation Level Dependent (TOLD) (2). Here, we explore the quantitative relationship between these techniques in assessing tumor oxygenation in response to hyperoxic gas breathing in human lung tumors growing in rats.

**Methods:** Cells of the the human lung tumor line A549 were implanted subcutaneously in the thigh of nude rats and allowed to grow to 1 cm diameter. Rats were anesthetized using isoflurane and maintained under general anesthesia (air and 1.5% isoflurane). 50  $\mu$ l hexafluorobenzene were injected directly into tumors in a fan pattern in a single plane, as recommended by Zhao et al. (3). MRI was performed using a <sup>1</sup>H/<sup>19</sup>F tunable volume coil placed around the tumor on a 4.7 T Varian system. Following shimming on the proton water signal, <sup>19</sup>F MRI was performed using the FREDOM approach to map  $pO_2$  during air breathing and repeated at the end of the experiment during hyperoxic (carbogen or pure oxygen) gas breathing. A series of interleaved  $T_1$ -(TOLD) and  $T_2^*$ -(BOLD) weighted proton (water) images were acquired during the transition from air to hyperoxic gas breathing. Data analysis was carried out on a voxel-by-voxel basis with IDL based house made



software.

**Results:** FREDOM approach showed a significant increase in  $pO_2$  values for A549 lung tumors from air (mean  $pO_2 = 23 \pm 3$  Torr) to hyperoxic gas breathing (mean  $pO_2 = 123 \pm 16$  Torr). BOLD and TOLD also depicted significant response upon oxygen challenge (mean maximum  $\Delta SI$  (%) =  $7 \pm 1$  for BOLD and mean maximum  $\Delta SI$  (%) =  $25 \pm 12$  for TOLD). A good correlation was found between  $pO_2$  during hyperoxic gas breathing and TOLD response (figure 2). However, no such correlation was found between  $pO_2$  values during hyperoxic gas breathing and changes in BOLD.



**Discussion:** The FREDOM approach has been used for many years to quantitatively assess tumor oxygenation by MRI. However, its widespread use has been hindered by the lack of <sup>19</sup>F capability of majority of research and clinical MR scanners. On the other hand, TOLD is a noninvasive technique based in shortening on the tissue water  $T_1$  due to dissolved molecular oxygen and directly applicable to the clinic. Here, we found a direct relationship between  $pO_2$  values measured using FREDOM and response with TOLD during hyperoxic gas breathing. These results are in good agreement with previous data in prostate tumor lines (4). Nevertheless, it is the first time these approaches are compared in the same animal.

**Bibliography:** (1) Tatum, J.L., Kelloff, G.J. and others.; *Int.J Radiat.Biol.* 2006;82:699-757. (2) Matsumoto K, Bernardo M, and others.; *Magn Reson. Med.* 56, 240-6, 2006. (3) Zhao, D., Jiang, L. and others.; *Methods Enzymol.* 2004;386:378-418. (4) Pacheco-Torres, J., Zhao, D. and others.; *International Society for Magnetic Resonance in Medicine.* 2008.