# MR characterization of the tumor microenvironment after arsenic trioxide treatment: evidence for an effect on oxygen consumption that radiosensitizes solid tumors

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## Introduction

The partial pressure of oxygen ($pO_2$) is a crucial factor affecting the response of tumors to irradiation and other cytotoxic treatments. It has been predicted that modification of oxygen consumption is much more efficient at alleviating hypoxia than modification of oxygen delivery.

Arsenic has been reported to have anti-tumor effect in acute promyelocytic leukemia and in solid tumors. $As_2O_3$ seems also to inhibit mitochondrial respiratory function in human leukemia cells. Thus, we hypothesized that $As_2O_3$ could be an important modulator of tumor oxygenation by affecting the oxygen consumption of tumors. We characterize the evolution of the tumor micro-environment after $As_2O_3$ treatment.

## Materials and methods

The effect of $As_2O_3$ (5 mg/kg) was studied in a transplantable liver tumor model (TLT) and in a Lewis Lung Caecinoma (LLC). Local $pO_2$ was measured in vivo using low frequency EPR (1) and $^{19}$F-relaxometry (2). The oxygen consumption rate was measured in vitro using high-frequency EPR. At the maximum $pO_2$ (after 1h30) perfusion and radiation sensitivity were also studied by Patent Blue staining assay and regrowth delay experiment after X-Ray irradiation (10Gy), respectively.

## Results

The administration of $As_2O_3$ increases significantly the $pO_2$ (measured by EPR) in TLT and LLC tumors, an effect that was not observed for the control group (Fig.1). The results were confirmed by $^{19}$F NMR relaxometry. The increase in $pO_2$ induced by $As_2O_3$ was not due to an increase in tumor perfusion as shown by the Patent blue staining assay (Fig.2). As the increase in $pO_2$ was not due to an increase in perfusion, the tumor oxygen consumption was investigated. The administration of $As_2O_3$ significantly decreased the rate of oxygen consumption (Fig.3). Finally, the irradiation (10Gy) of tumors showed a regrowth delay that was significantly increased in arsenic-treated mice.

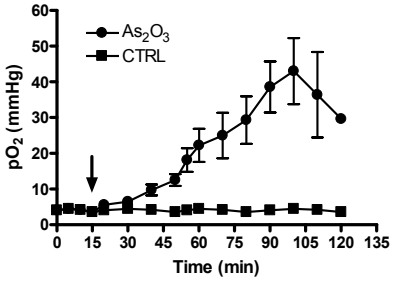


Fig.1: Tumor $pO_2$ measured by EPR oximetry in TLT tumors as a function of time. Arrows, injection time of the drug.

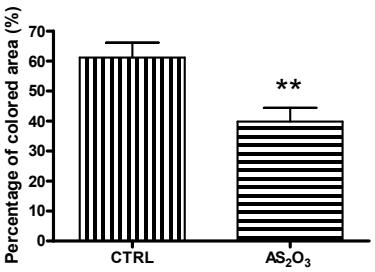


Fig. 2: Effect of $As_2O_3$ on blood perfusion measured by the Patent blue staining.

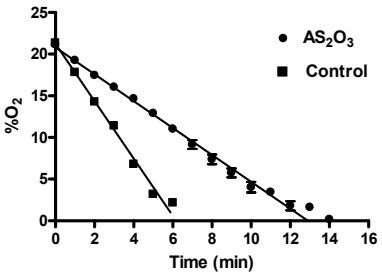


Fig. 3: Effect of $As_2O_3$ administration on tumor oxygen consumption rate in TLT tumor cells.

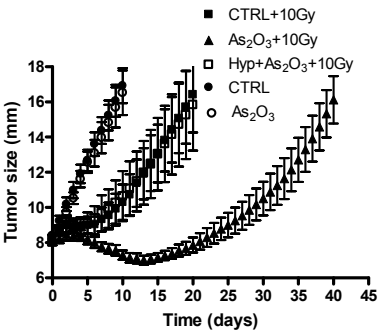


Fig. 4: Effect of $As_2O_3$ and radiation on TLT tumor regrowth.

## Conclusion

Arsenic trioxide is an important modulator of $pO_2$ by decreasing oxygen consumption and enhances the response of tumors to radiotherapy. The time-window for the radiosensitization effect by $As_2O_3$ can be predicted using MR oximetry techniques (EPR or $^{19}$F NMR relaxometry)

**References** (1) Gallez et al, NMR Biomed. 2004, 17,240-262. (2) Jordan et al, MRM 2009, 61, 634-638.