Imaging tumor extracellular pH using PET/MRI co-agents

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Introduction

Acidosis is a useful biomarker for tumor diagnoses and for evaluating early response to anti-cancer treatments.[1] Despite these useful applications, there are few methods available for non-invasively measuring tumor extracellular pH (pHe), and none are routinely used in clinics.[2] Responsive MRI contrast agents have been developed, and they undergo a change in MRI signal with pH. However, these signal changes are concentration-dependent, and it is difficult to accurately measure the concentration of an MRI contrast agent in vivo.[3] PET/MRI provides a unique opportunity to overcome this concentration dependence issue by using the PET component to report on the concentration of the pH-responsive MRI agent.[4,5]

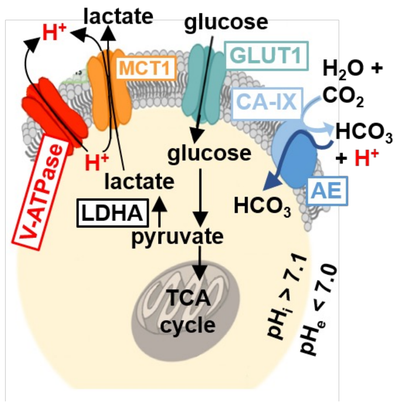


Figure 1. Cells produce pyruvate from glucose which can then be transformed into lactate through aerobic glycolysis or broken down to produce a large amount of ATP through oxidative phosphorylation. Even in the presence of oxygen, cancer cells have upregulated aerobic glycolysis, leading to lactate and H^+ ions being shuttled out of the cell that causes a decrease in pHe. Figure Adapted from Chen et. al[1]

MRI Phantom preparation

$$pH = pKa + log\frac{r_1 - a}{b - r_1}$$

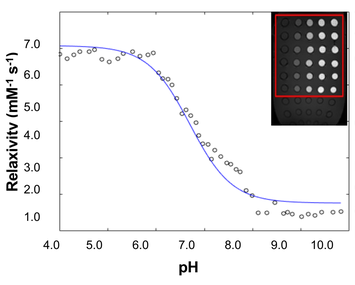
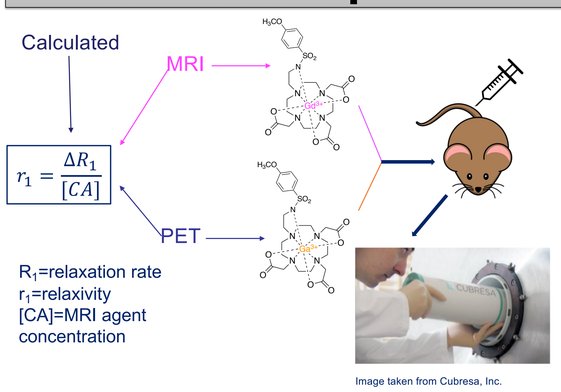


Figure 2. Phantom holders are prepared for high-throughput T_1-weighted MR imaging. Samples are prepared in varying concentrations and pH values, and the relaxation rate of each tube is calculated from the measured T_1 time. The r_1 relaxivity of the agent is determined from the slope of the concentration-relaxation rate graphs. The r_1 of the MRI co-agent depends on pH at 7T, and more samples will be prepared to fill in the graph from pH 6-8.

PET/MRI co-agents can measure pH *in vivo*



Goal: To develop and apply a PET/MRI contrast agent that measures pH with an accuracy and precision <0.1 pH unit

Simultaneous ^{18}F PET/MRI can measure tumor extracellular pH

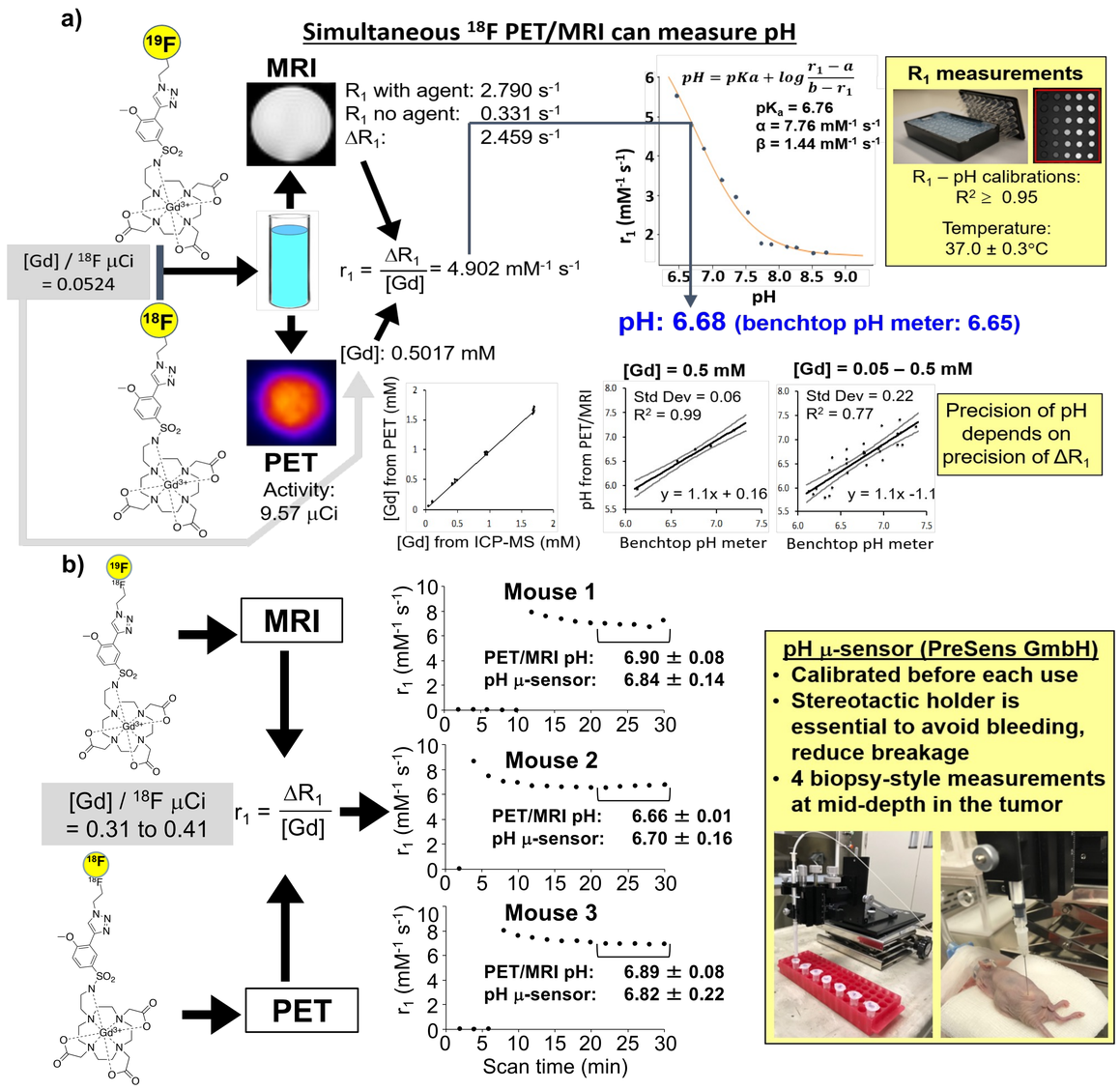
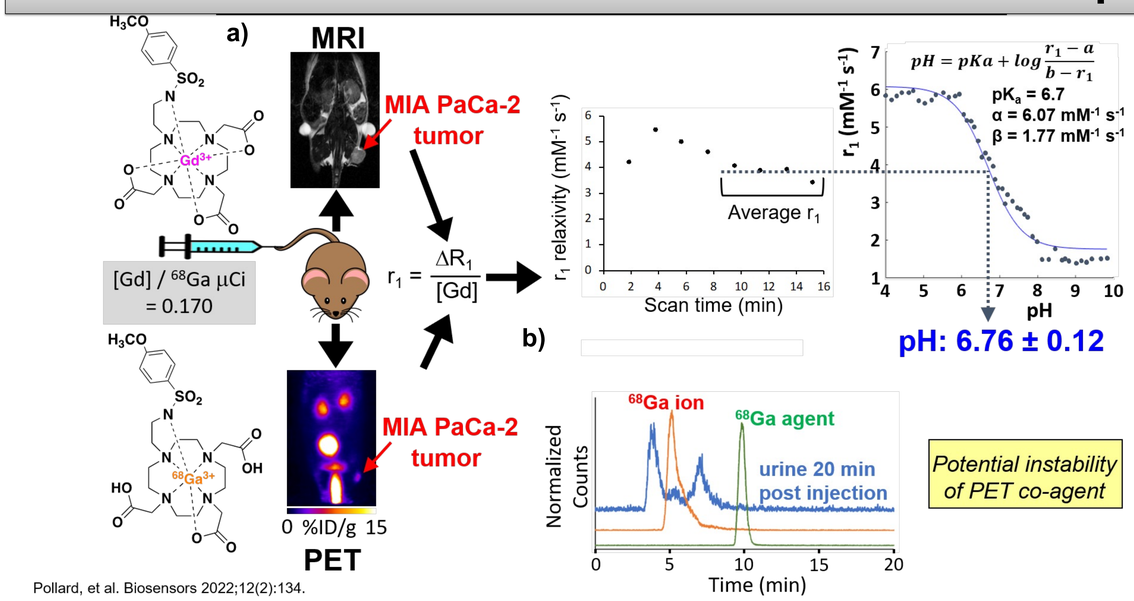


Figure 3. ***^{18}F PET/MRI co-agents can measure tumor pHe in vivo.***
a) The activity of the PET co-agent was used to estimate the concentration of the MRI co-agent, based on the [Gd] / μCi ratio initially introduced to the sample. ΔR_1 and [Gd] were used to estimate r_1 relaxivity. The r_1 was converted to pH using a carefully measured, pre-determined calibration, which matched the pH measured with a benchtop pH meter. The standard deviation of the pH measurement was dependent on the concentration of the MRI contrast agent, indicating that the precision of the pH estimate depends on the precision of ΔR_1 measurement.
b)Tumor pHe measurements were determined from dynamic PET/MRI scans. Once the curve reached steady state, the average pH value was calculated and compared to measurements from a pH microsensor. A correlation of 0.848 was achieved between the two methods. Data points at a pH of "0" on the graphs represent time points where there was inadequate agent concentration in the tumor to measure pHe.

Simultaneous ^{68}Ga PET/MRI can measure tumor extracellular pH



Pollard, et al. Biosensors 2022;12(2):134.

Figure 4. ***^{68}Ga PET/MRI co-agents can measure tumor pHe in vivo.*** a) A simultaneous DCE MRI and dynamic PET scan were obtained. The change in relaxation rate was determined from the MR images. The concentration of the MRI co-agent was determined from the %ID of the PET image along with the known injected ratio of the two agents. These values were used to calculate r_1 relaxivity in two-minute time frames during the dynamic PET/MRI scan. Once the curve reached a steady value, the average r_1 was used to estimate tumor pHe using an experimental r_1-pH calibration fit with a modified Henderson-Hasselbach equation. b) At the end of the PET/MRI scan, the mice were sacrificed, and urine, blood, and tumor were removed. Urine was analyzed with radioHPLC, which showed no presence of intact ^{68}Ga co-agent, indicating potential *in vivo* instability of the PET co-agent.

Simultaneous ^{64}Cu PET/MRI was unable to measure tumor extracellular pH

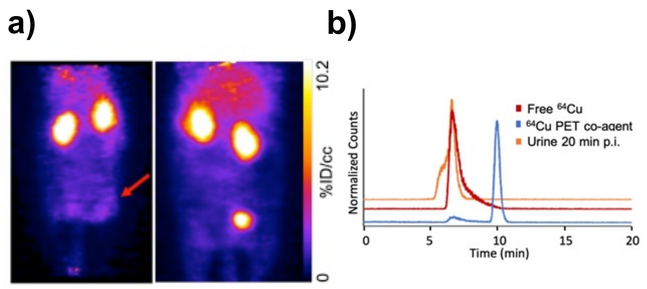


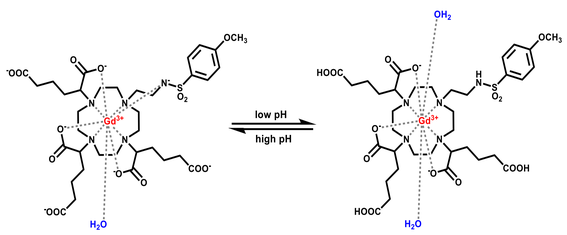
Figure 5. ***The ^{64}Cu PET co-agent demonstrated in vivo instability.*** **a)** A PET image from a dynamic PET/MRI scan using the ^{64}Cu PET co-agent showed poor tumor uptake and high liver uptake. **b)** RadioHPLC of urine collected from a mouse after a dynamic PET/MRI scan showed the presence of only free ^{64}Cu, indicating *in vivo* instability of the ^{64}Cu PET co-agent.

Conclusions

- These preliminary results showed that tumor acidosis can be evaluated with simultaneous PET/MRI.
- The **^{18}F PET/MRI** co-agents showed the most promising approach. Improvements are needed to more precisely measure MRI r_1 relaxation rates, and to ensure the in vivo stability of the agents.

Future PET/MRI co-agents

- Develop a ^{86}Y chelate for PET co-agent (14.7 hours half-life, can be shipped overnight)
- Add ligands to improve biocompatibility and solubility, especially at low pH
- Develop PET/MR Fingerprinting to improve the precision of the ΔR_1 measurement



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