Ex vivo Bio-orthogonal MRI imaging – A novel method proposed for metastatic cancer detection

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Introduction: Metastatic tumors (METs) are responsible for the death of about 90% of cancer patients with solid tumors[1]. METs can be as small as 0.125μL in volume. Due to the small sizes of METs, conventional imaging produces many false positive diagnoses. This research uses two simultaneous detection methods, both of which must be positive for identification of a MET. When the detection methods are "orthogonal" to each other (not projecting one onto the other) then the occurrence of a false diagnosis is reduced significantly. Two Magnetic Resonance Imaging (MRI) contrast agents, Iron-Oxide particles (IOP) and Gadolinium (Gd), were hypothesized to be orthogonally detectable using T2* and T1 scans, respectively. Previous studies have shown that Gd and IOP can be detected orthogonally in gel phantoms, shown signs of promise in excised tissue. These studies are to show the proportionate ratios in which Gd and IOP can be orthogonally detected.

Materials and Methods: 3T Siemens instrument with a 12 channel Magnetom head coil was used at the BYU MRI facility to image with T1 and T2* scans. Parameters for 3D T1 weighted GRE scan were TR/TE = 200/5ms, flip angle was 90°, and matrix size was 64 x 64 with a slice thickness of 1.25mm and field of view of 128 x 128 mm. Parameters for the T2* weighted GRE scan were TR/TE = 11/5ms, flip angle was 25°, and the same field of view and resolution as the T1 weighted scan were used.
A piece of porcine fat received two rows of injections, the first with a constant concentration of IOP at 0.2mM and factor of five diminishing concentrations of Gd from 5mM to 0.008mM as seen in Figure 1a. The opposite was done with the second row where Gd was constant and diminishing concentrations of IOP were administered. Reference vials containing injected concentrations of Gd and IOP lined the top and bottom of the tray. Methylene blue was mixed with injections before administration and used as a dye to visually track the injections in the fat.

Results and Discussion: As seen in Figure 1b and 1c, it was observed that white (positive) contrast was added to T1 scans in locations where the concentration of Gd was high enough, whereas black (negative) contrast was added to T2* scans in the locations where the concentration of IOP was high. This supported our hypothesis since positive contrast was not seen from Gd on T2* scans yet IOP did not cancel out the T1 scans with negative contrast. The visibility of contrast from each agent in their respective scans shows independence, and thus bio-orthogonality. The local concentrations could not be readily determined from the data taken.

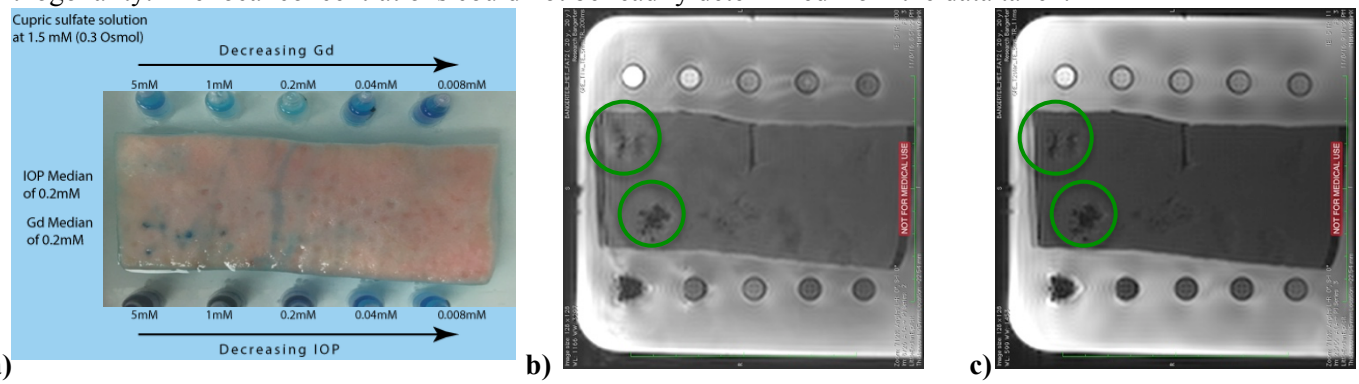

Figure 1- a) Schematic of injection experiment with picture of actual set-up overlain, **b)** T1 image showing positive enhancement where Gd was at a high enough concentration, **c)** T2*image showing negative enhancement where IOP was at a high enough concentration.

Conclusions: It was shown that Gd and IOP can be imaged independent of each other on their respective scans in the same location. This proves that these two agents are bio-orthogonally detectable in excised tissue. This is crucial to the future of MET detection with MRI. If these agents can be delivered directly to the cancer site in the body it is very plausible that MRI scans can confirm the location of the site with much greater accuracy than conventional methods. However, it was undetermined what the optimal ratio of Gd to IOP is in addition to the preferred concentrations to produce the bio-orthogonal effect. It is left to the future work of this project to determine those values.

References: [1] P. Mehlen and A. Puisieux, "Metastasis: a question of life or death,"*Nat Rev Cancer*, vol. 6, no. 6, pp. 449–458, Jun. 2006.