Purpose: Early detection of colon cancer can vastly improve outcomes. Targeted contrast agents that specifically enhance early cancers could significantly improve diagnostic accuracy. Here we compare a new MRI contrast agent that is sensitive to glycolysis to a conventional Gd-based agent. Specifically, we report on: (1) MRI using Gd and a cancer specific, vanadium-based agent (VC) to measure contrast improvement in vivo, (2) a novel method of co-registration of in vivo and ex vivo images using agar-based phantoms, and (3) X-ray fluorescence microscopy (XFM) to quantify contrast uptake directly and to determine cellular and sub-cellular distributions in situ.

Methods: Colonic tumors were induced in C57I female mice (n=25) with i.p. injection of azoxymethane weekly for 2 weeks (10 mg/kg), followed by 2 cycles of 2.5% dextran sulfate sodium in the drinking water for 5 days. This model mimics many clinical and pathological features of colitis-associated colon cancer. T1/T2-weighted and contrast-enhanced MR images were acquired using a 9.4 Tesla Bruker scanner. A flexible tube (2 mm o.d.) composed of five 4-5 mm-segments of color-coded agar containing different Gd concentrations was inserted into the rectum, extending up to the cecum. Immediately after sacrifice at the end of in vivo MRI experiments, the colons were excised with the fiducial marker in place. This agar-based phantom provided a visible fiducial marker on in vivo MR images and served as a ruler for precise co-registration of pathological features detected on MR images with histological morphology. The day after the last in vivo MRI, mice were sacrificed after Gd and/or VC injection I.V. (0.13 mmol/kg), colons (normal and tumors) were harvested and ~5 μm thick slices were sectioned for XFM and H&E. XFM images (0.3 - 10 micron in-plane resolution) were acquired using an X-ray microprobe at the Advanced Photon Source at the Argonne National Lab. Concentrations of metal ions and other elements were determined based on the tissue thickness on the slide.

Results: Locations of tumors along the colon were precisely determined on the basis of agar-based, visible fiducial marker, as seen in the figure below. Values of T2 distinguished normal colon from colonic wall focally thickened with tumor (p<0.005). From DCEMRI, the values of Ktrans (min⁻¹) were found to be 0.12±0.01 for normal colon and 0.61±0.05 for tumors (p<0.001). For VC uptake in implanted rodent tumors, relative peak enhancements in tumor and muscle of 0.225 ± 0.052 and 0.05 ± 0.018, respectively, were measured during the injection phase - a nearly 5-fold increase in enhancement between tumor and muscle with p < 0.001. VC enhanced specific regions of tumors selectively in MR images, with enhancements typically greater than 50% and often as high as 100%, while no enhancement for Gd. XFM images (0.3 micron) scans of tumors revealed that VC accumulates in the intracellular space in cancers; the uptake of VC in cancer cells is ~8-fold higher compared to the background VC signal.

Conclusions: There are potential advantages of using VC-based contrast agents. These compounds have very low toxicity and thus could be used repeatedly at concentrations that produces strong MRI contrast. VC-based agents preferentially accumulate inside of cancer cells, offering an advantage over less selective Gd-based agents. MRI and XFM studies of early colon cancer in mice may improve early detection strategies, provide increased understanding of cancer progression and improve assessment of therapeutic responses.