MnMRI of Pancreatic Cancer

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TARGET AUDIENCE: Clinical and basic science researchers interested looking for alternative imaging paradigms and experimental models to study the development and progression of pancreatic cancer in animal models.

PURPOSE: Pancreatic cancer is the fourth most common cause of cancer-related deaths in the USA in both men and women. Detection of pancreatic adenocarcinoma at an early stage is difficult due to the lack of specific symptoms. Due to the generally late diagnosis of this tumor, little is known of the origins of this tumor and how this tumor progresses in the early stages of the disease. Non-invasive accurate detection of pancreatic cancer remains a challenge despite continuous advances in imaging technologies. Tumor growth and proliferation has been shown to involve the transport and regulation of calcium. For example T-type calcium channels are increasingly expressed during S phase of the cell cycle. This pattern is found in many cancers although at different stages of development. A recent study found a positive correlation between tumor cell proliferation rates and MEMRI R_1 relaxation time in cell pellets following exposure to Mn (Berkowitz, 2012). Several calcium-binding proteins are overexpressed in both early pancreatic lesions (PanIN) as well as PDACs. Similarly, commonly used PDAC cell lines such have higher expression of genes regulating Ca uptake and binding, including several genes of S100 Ca binding protein family. Their expression is directly related to proliferation and based on Braun et al. is a reasonable target for imaging cancer cell proliferation using Mn incorporation

METHODS: We developed and tested an orthotopic PDAC mouse model (Fig 1) where luciferase expressing $1x10^6$ BxPC3 human pancreatic cells were injected in the tail/body of the mouse pancreas and tracked in-vivo via 2D and 3D bioluminescence (BLI) and high-resolution anatomical MRI (Figure 1). MnCl2 was administered IP 2x per day for two days. T1 maps of control and Mn tumors were generated based on the MnMRI (Figure 1). Tissue samples were obtained and analyzed for elemental content with X-ray fluorescence microscopy (XFM) (Figure 2).

RESULTS:

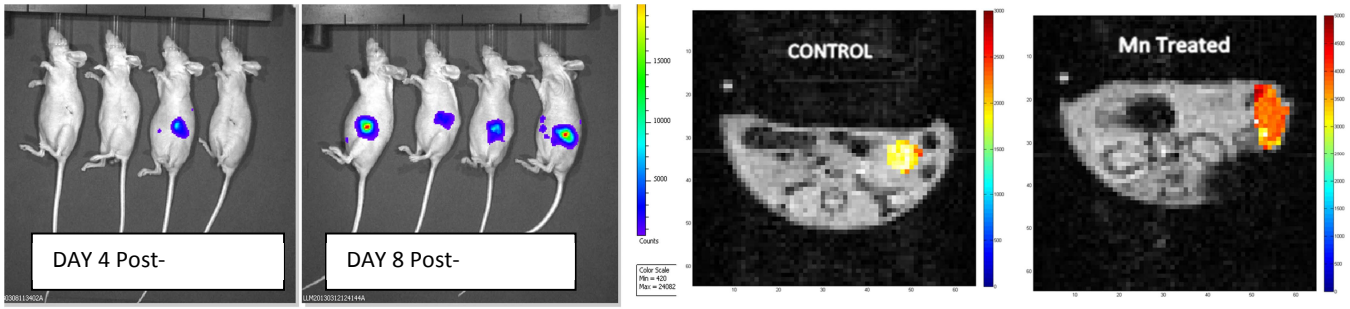

Figure 1. Bioluminesence imaging (BLI) and MnMRI of orthotopic pancreatic tumors. Panel A (Left) illustrates the developing tumors and the increasing BLI signal indicating increasing tumor load. **Panel B** (Right) illustrates two mice with control or Mn treatment. The color overlay was generated from the T1 maps of the tumor demonstrating a decrease in T1 from 3.6 sec in control to 1.0 s in Mn treated indicating a preferential increase in Mn accumulation.

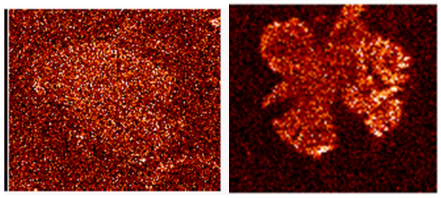

Figure 2 XFM Images of Mn Content. Isolated tumors from control (left) and Mn treated tumors (right) demonstrating Mn uptake responsible for increased contrast

DISCUSSION: These data confirm that Mn is taken up by developing pancreatic cancers and provides functional information about tumor development. This approach holds promise in providing early detection of developing lesions and a functional output to gauge therapy.

CONCLUSION: We have developed MnMRI, to study an orthotopic PDAC mouse model (Fig 1) using human pancreatic cells. Tumor development was succesfully tracked in-vivo via 2D and 3D bioluminescence (BLI), high resolution anatomical and functional MRI/MnMRI. XFM confirmed increased Mn uptake in the treated tumor. This approach will be useful for studying the many murine models of human PDAC.

REFERENCES: Braun RD, Bissig D, North R, Vistisen KS, Berkowitz BA (2012) Human Tumor Cell Proliferation Evaluated Using Manganese-Enhanced MRI. PLoS ONE 7(2): e30572. doi:10.1371/journal.pone.0030572