In vivo cellular MRI monitoring of FeO Labeled DC-based cancer vaccine for immunotherapeutic treatment of pancreatic cancer

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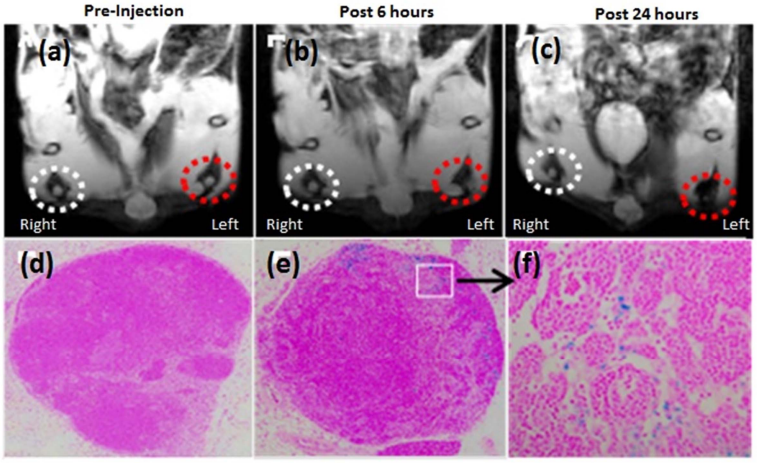
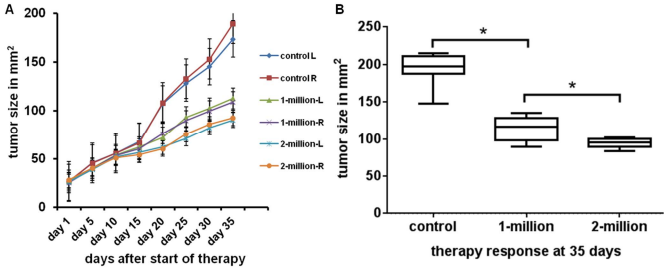
PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of U.S. cancer-related mortality. Currently, patients with PDAC have a dismal prognosis due to a complete lack of effective therapies [1]. Dendritic cells (DC) are one of the most potent antigen-presenting cells (APCs) in the immune system. Development of therapeutic cancer vaccines using DCs loaded with tumor antigens which are transferred to a host enhancing its tumor immune response, is a viable treatment option, however clinical trials have failed to achieve good efficacy[2]. One of the major roadblocks to the development of these immune therapies **is the inability to assess effective target acquisition**. In this work we demonstrate that ironoxide labeled DCs, loaded with antigens, can be effectively tracked as they "home in" on the lymph nodes [3] . By providing direct MR visualization of DC uptake in lymph node environment one can positively confirm target acquisition and explore the underlying mechanisms more in depth, The research conducted in this work will the development of these cancer vaccines for translational applications

METHODS Panc-2 tumor cells (~2 × 10^6 cells) were implanted in both right and left flank female C57BL/6 mice and allowed to grow to palpable nodule (~3-5 mm). Bone marrow derived DCs were prepared as described in [1]. After antigen loading as described in [2-3] DCs were labeled with biocompatible iron nanoparticles FeOLabel-TexasRed (GENOVIS AB, Lund Sweden) as prescribed. Characterization was conducted to evaluate percent of iron and viability of labeled DCs. Iron amount was estimated by MR relaxometry using variable concentration phantoms (0-10 μg/ml). Vaccine administration was performed by injecting the labeled DCs in the left hind footpad of the mice (Three groups: 1) 1e6 cells, 2) 2e6 cells and 3) no cells as control) All MRI experiments (in vitro and ex vivo) were carried out on a Bruker 7 T (Clinscan, Ettlingen, Germany) using multiple spin echo and multiple gradient echo sequences to obtain coronal and axial images of the bilateral popliteal LNs and to generate corresponding parametric maps (Slice Thickness=0.2 mm In plane resolution 0.14 mm) . Animals were scanned at 6 hours and 24 hours after injection of DCs. All physiological parameters were maintained during experiments as prescribed by institutional ACUC standards. Ex vivo assessment of DC loading in popliteal LN was conducted using histological methods for validation of MRI images. Anti-Tumor efficacy of DCs was evaluated using standard vital signs and by measuring tumor volume at different time points following tumor implantation (1,5,10,15,20,25,35 days).

RESULTS & DISCUSSION: Shown in Figure 1(a-c) are three coronal T2W images of bilateral popliteal LN's at different times (a) preinjection of DC's, (b) 6 hour post and (c) 24 hour post. The left LN exhibits clear signal decrease consistent with migration of iron labeled DC's (injected in left footpad) while right is unaffected. Prussian blue staining of bilateral popliteal LNs are shown in Fig 1 (d) Right and Fig 1(e) Left, confirming presence of SPIO labeled DC's in the later (Fig 1(f) is a blow up of region). Also shown in Fig 2 are the tumor size longitudinal measurements for control group compared to group A (1e6 DC's) and group B (2e6 DC's) demonstrating the therapeutic efficacy of the treatment





CONCLUSION Preclinical in vivo testing of novel therapies is particularly relevant for the development of advanced treatments such as immune based therapies. The ability to track target acquisition by DC's labeled with FeO and loaded with tumor antigen can open new avenues to investigate interaction of these cells with a real biological environment. We have shown how MRI confirmed target acquisition (lymphnode uptake) was well correlated with therapeutic response

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