Tracking Chemotherapy-Induced Changes in Tumor Antigen Expression in a Pre-Clinical Breast Cancer Model

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Background. A key goal of cancer research is to be able to monitor and predict the response to treatment. Considering the variability of the response, this has to be accomplished on a patient-by-patient basis. With this in mind, we applied magnetic resonance imaging to monitor the expression of a tumor-specific antigen (uMUC-1), found on over 90% of breast cancers and predictive of chemotherapeutic response. As a contrast agent, we employed an imaging probe (MN-EPPT) targeting uMUC-1. MN-EPPT consists of superparamagnetic iron oxide nanoparticles (MN) for MR imaging, modified with Cy5.5 dye (for fluorescence optical imaging), and conjugated to peptides (EPPT), specifically recognizing uMUC-1 (1,2).

Methods and Materials. *In vitro studies.* We treated BT-20 human breast adenocarcinoma cells with doxorubicin (0.4 μM) or PBS, as a control, for 48-hrs. Following treatment, we incubated the cells overnight with either MN-EPPT or a scrambled control probe, MN-SCR (50 μg Fe/ml). We analyzed probe uptake in MRI phantom studies. *In vivo studies.* We treated mice bearing orthotopic human breast carcinomas with doxorubicin (7mg/kg) or saline once a week over the course of two weeks. We performed magnetic resonance imaging (MRI) one day prior to the beginning and one day after the completion of treatment, before (pre-contrast) and 24 hrs after (post-contrast) i.v. injection of MN-EPPT or MN-SCR (10mg Fe/kg). For both in vitro and in vivo imaging we used a 9.4T Bruker horizontal bore scanner (Billerica, MA) equipped with ParaVision 3.0 software. The imaging protocol consisted of transverse T2-weighted spin echo (SE) pulse sequences. To produce T2 maps for quantitative analysis of probe accumulation, the following imaging parameters were used: SE TR/TE = 3000/ [8, 16, 24, 32, 40, 48, 56, 64]; FOV = 40 x40 mm^2; matrix size = 128 x 128; slice thickness = 0.5 mm; in-plane resolution = 312x312 μm^2.

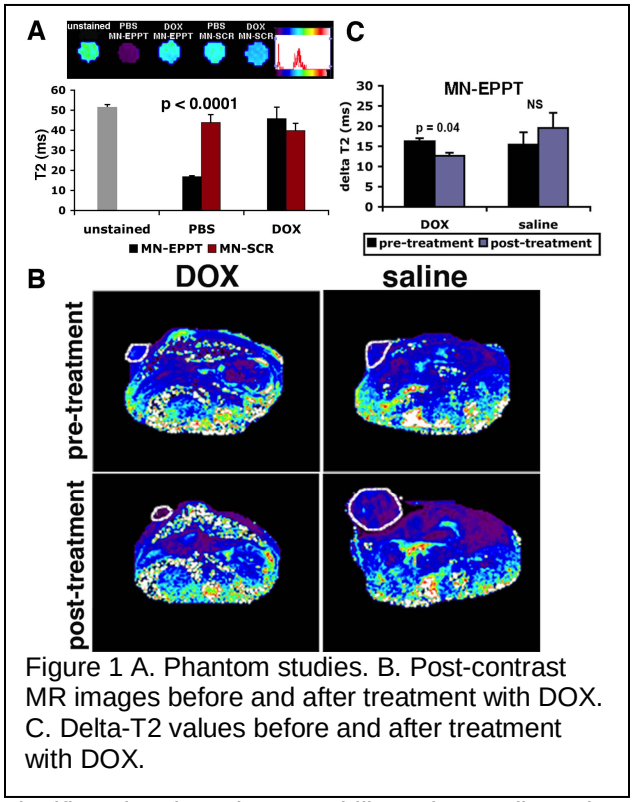

Figure 1 A. Phantom studies. B. Post-contrast MR images before and after treatment with DOX. C. Delta-T2 values before and after treatment with DOX.

Results. Treatment with doxorubicin in vitro led to downregulation of uMUC-1 expression in BT-20 cells. This change was reflected by a significant increase in the T2 relaxation times of the cells, when MN-EPPT was used as a contrast agent. The cellular uptake of MN-SCR was marginal and was not affected by treatment with doxorubicin (Figure 1A). In vivo, in mice injected with MN-EPPT, tumor delta-T2 was significantly reduced after treatment with doxorubicin, indicating a lower accumulation of MN-EPPT and reflecting the reduced expression of uMUC-1. In mice treated with saline or injected with MN-SCR as a contrast agent, delta-T2 values were not different before and after treatment with doxorubicin (Figure 1B and C).

Summary. These studies suggest that it is feasible to track changes in target antigen availability by MRI and illustrate the value of this approach for monitoring the progress of chemotherapy on a molecular scale. This approach may ultimately become applicable in a clinical setting and has the potential of significantly advancing our ability to better direct the development of molecularly-targeted individualized therapy protocols.

References.

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