Hypothesis: Precise three dimensional control of therapeutic ultrasound can be exploited to enhance cancer drug delivery.

Methods: Relevant parameters include the following: 16-element annular ultrasound array integrated with high speed motors, transducer diameter: 45 mm, radius of curvature: 35mm, acoustic efficiency > 85%, power rating: 50W, focal spot size (approx.): 1.5mm x 1.5mm x 2mm. Multiple planes of MR acquisition are sent in real time from the Bruker 70/30USR Biospin to the Thermoguide (Image Guided Therapy- IGT) thermal controller. The IGT system has multiple embedded algorithms for temperature estimation, motion correction and temperature display. In our study, temperature estimation was performed by a simple proton resonance frequency shift algorithm. With a Luxtron fiberoptic probe, we first validated ultrasound-induced temperature changes produced by 3-MHz ultrasound. A light spiral trajectory was directed to a 3 mm ROI, increasing the temperature by 2-9ºC. For in vivo studies approved by the UC Davis Animal Use and Care Committee, we applied therapeutic ultrasound (1.5 MHz, 2 minutes, 32% duty cycle adjusted to maintain temperature, 1.3 MPa, temperature increase of 5ºC) within tumors in the Met-1 mouse under ultrasound guidance. Fusion with PET was used to measure the accumulation of drug delivery vehicles, where MRI and PET image spaces are aligned by fiducial-based registration. For PET imaging, we have developed a surface chelation labeling method using 64Cu (half life = 12.7 h), where 64Cu is added to preformed particles which contain BAT(6-[p-(bromoacetamido)benzyl]-1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid)-lipids. This method provides fast and simple labeling of particles with 64Cu.

Results: Using a 3 mm spiral trajectory, temperature increases of 2-9ºC were created using ultrasound (Fig. 1a-c). Insonation of ex vivo turkey breast demonstrated a localized temperature increase in the insonified region of interest (Fig. 1b-c). The phase and resulting temperature estimate maps (Fig. 1b-d) acquired using a TE of 7.4 ms correlated with the temperature increase as measured by the Luxtron (Fig. 1a). Preliminary studies insonifying the Met-1 tumor (Fig. 1e) with 1.5-MHz ultrasound demonstrated greater than 2-fold enhancement in the accumulation of PET-labeled vehicles in tumors using PET, achieving concentrations as high as 20% injected dose/gram-tumor (Fig. 1f, where the insonified region of interest is shown with an arrow).

Conclusion: We found that real time MR control of hyperthermia is feasible at high field with a temperature accuracy on the order of 1ºC. Local ultrasound hyperthermia can significantly increase the local accumulation of drug delivery vehicles within the Met-1 tumor; additional studies will be described using insonation of doxorubicin-loaded particles under MR guidance.

Fig. 1. Preliminary evaluation of MR temperature mapping at high field and the use of ultrasound to enhance drug delivery. (a) Temperature validation using the Luxtron during spiral US trajectories with 1, 2, or 4 acoustic Watts of transmission for 2 minutes. Small artifacts are observed as the US scans over the Luxtron. (b-c) Phase map (b) and magnitude image (c) with temperature overlay from IGT system resulting from FLASH sequence applied to turkey breast with TR of 44.7 ms, TE of 7.4 ms, FA 10º, matrix 128x64, slice thickness 2 mm, FOV 8 cm. Ultrasound (3 MHz, 4W) was scanned in 3 mm spiral pattern. Temperature elevation was spatially mapped. (d) Subset of phase images acquired over 3 minutes before, during and after insonation applied starting in frame 3 above, insonation ended in frame 9. (e) Representative MR slice from a 3-minute 20-slice scan mapping location of tumor and surrounding structures to plan acoustic therapy in live Met-1 tumor mouse. Scan used 200 mm gradient set, circularly polarized 15.4 cm transmit coil in quadrature mode, rat brain 4-element phased array coil on receive with fat and motion suppression applied and the following parameters: TR 450 ms, TE 7.1 ms, FOV 4.3x2.3 cm, 0.17 x 0.25 x 0.65 mm3 voxels. Red scale bar 5 mm, yellow arrow indicates Met-1 tumor implanted within mammary fat pad. (f) PET images acquired from Met-1 mouse after injection with 64Cu-labeled particles and tumor insonation (red arrow indicates insonified tumor).