Purpose: The underlying mechanism of non-thermal effects of pulsed high intensity focused ultrasound (pFUS) on normal and tumor tissues is not well understood. Our recent studies showed significant prostate cancer cell killing in vitro and significant prostate tumor growth delay in vivo after pFUS treatment. We hypothesized that these effects of non-thermal pFUS are due to an increase in cell apoptosis and decrease in cell proliferation. Therefore, the purpose of this study was to analyze the biomarkers of apoptosis and proliferation in prostate tumors after pFUS exposures.

Methods: An orthotopic prostate tumor model was established in nude mice. Prostate tumors were sonicated with MR guided pFUS (1MHz, 5W acoustic power, 5Hz frequency; 0.1 duty cycle) for 60 sec for each sonication with temperature <42°C (InSightec ExAblate 2000 with a 1.5T GE MR scanner). Untreated tumors were used as controls. The mice were sacrificed at predetermined times up to 7 days following therapy. Tumors were processed for light microscopic examination with H&E staining and immunohistochemical staining for caspase 3 (a marker of apoptosis) and Ki67 (a proliferation marker) expression.

Results: Light microscopy revealed the absence of thermal damage and acute destruction of tumor tissues exposed to pFUS. The microvessel walls in the tissues remained intact. There was no change in the extent of hemorrhage upon pFUS treatment over time. The apoptotic index, defined as a percentage of apoptotic cells per total number of cells, peaked at 24 hours after FUS treatment relative to control. There was no dramatic difference in the proliferation indices between different time points.

Conclusions: Our results suggested that non-thermal pulsed pFUS induced caspase 3-
mediated apoptosis and did not produce any thermal damage in the prostate tumor tissues. We are performing additional studies to evaluate blood vessel density and cellular DNA damage upon pFUS treatment.