Focused Ultrasound Foundation Progress Report - Final
Targeted Drug Delivery for Cancer Therapy

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Specific Aims 1 and 2

A total of 64 mice have been successfully treated with the Philips Sonalleve MR-guided focused ultrasound system to the completion of Aims 1 and 2.

KPC and orthotopic mice were assigned randomly into treatment and control groups, with 4 mice in each group. Two different doses of doxorubicin loaded thermosensitive liposomes (TSL), Thermodox (TDOX), were used: a dose of 15 mg/kg to facilitate detection and quantification of autofluorescence after treatment; and a clinically relevant dose of 5 mg doxorubicin/kg. Free doxorubicin was injected at both dosages. A non-thermosensitive PEGylated liposomal form of doxorubicin, Doxil, was also evaluated at 5 mg/kg dose. Mice were treated with or without MR-HIFU hyperthermia in combination with the doxorubicin based drug.

Tumor doxorubicin concentrations were evaluated using high performance liquid chromatography (HPLC) as µg doxorubicin per gram tissue. The most significant finding was observed in the KPC mice at a TDox dose of 15 mg/kg. In combination with hyperthermia treatment, there was a significant increase in tumor doxorubicin concentration compared to non-treated controls (Figure 1). It was found that free doxorubicin in combination with hyperthermia did not result in a significant increase in tumor drug concentration compared to without heat. The combination of hyperthermia and non-thermosensitive liposome (Doxil) also did not result in a significant increase in tumor doxorubicin concentration.

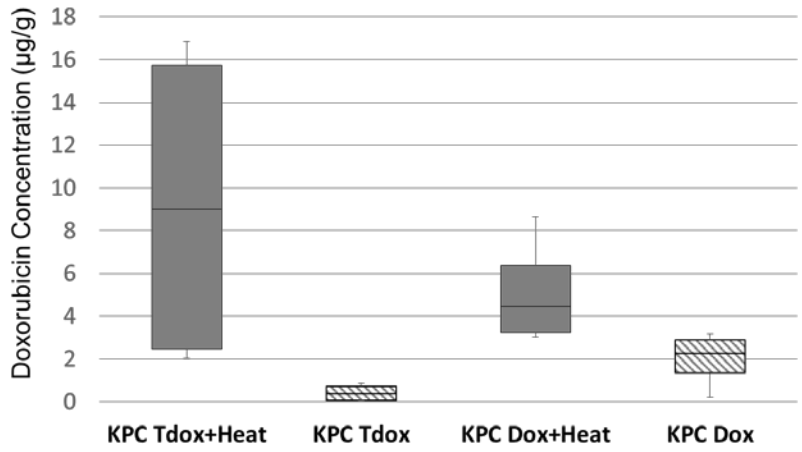

Figure 1. Box plot of KPC mice injected with either 15 mg/kg of Thermodox or free doxorubicin with and without hyperthermia treatment.

Specific Aims 3

In order to have clear understanding of tumor characteristics we have performed studies using the 14T MR System, (spectrometer with a micro imaging accessory, 600 MHz Bruker Avance III) to determine the tumor volume, diffusion and perfusion properties, and detecting abnormal tumor vasculature. The result of tumor characterization suggested that magnetization transfer ratio has a correlation (r=0.87) with the amount of stroma in the tumor. Additionally diffusion weighted imaging (DWI) provides useful information regarding tumor properties. Apparent diffusion coefficient (ADC) values has a negative correlation with the level of stroma in the tumor. The result of tumor characterization suggested that KPC model is the best model to study survival studies. ADC values of three different mouse model of pancreatic cancer are compared in Figure 2. Low diffusion rate in KPC model correlates with higher amount of stroma and mimics the human disease.

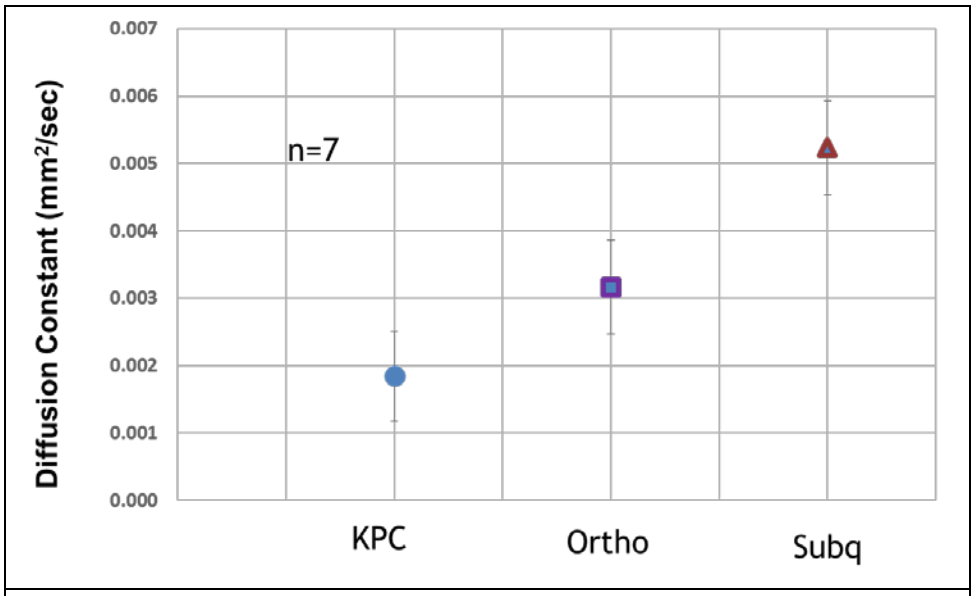

Figure 2. ADC value of KPC, orthotopic and subcutaneous pancreas cancer mice model.

Although there are some mice that are still being monitored, initial studies on KPC mice injected with 10mg/kg Thermodox treated with MR-guided focused ultrasound hyperthermia showed a slower tumor growth rate compared to the animal that was only injected with drug, Figure 3.

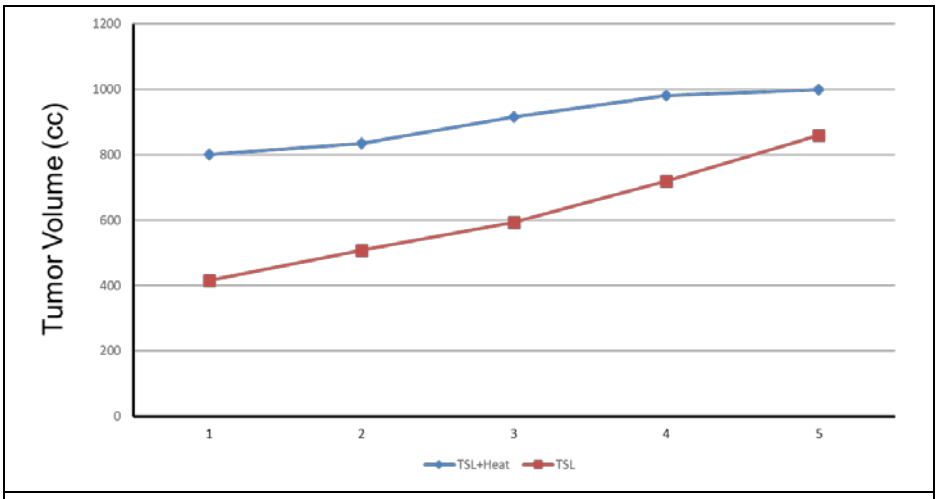

Figure 3. Tumor growth curve.

Summary

Overall results of this study show the potential for a positive effect of MR-HIFU hyperthermia on drug delivery.

Presentations:

Farr N, Wang YN, Partanen A, D'Andrea S, Lee DH, Pillarisetty V, Starr F, Hwang JH. MR-guided focused ultrasound induced hyperthermia for enhancing drug delivery in a pancreatic cancer mouse model: a feasibility study. 12th International Symposium on Therapeutic Ultrasound, June 12, 2012. Heidelberg, Germany.

Farr N, Hijnen N, Keepkens E, Wang YN, D'Andrea S, Lee DH, Grull H, Hwang JH. MR-guided focused ultrasound induced hyperthermia for enhancing drug delivery in a pancreatic cancer mouse model. Focused Ultrasound Symposium, October 17, 2012. Bethesda, MD.

Farr N, Wang YN, D'Andrea S, Lee DH, Hwang JH. MR-guided focused ultrasound induced hyperthermia for enhancing drug delivery in a pancreatic cancer mouse model. Oral Presentation. 13th International Symposium of Therapeutic Ultrasound, May 13, 2013. Shanghai, China.

Farr N, Wang YN, D'Andrea S, Lee DH, Hwang JH. Hyperthermia triggered drug delivery in a pancreatic cancer mouse model using MR-guided focused ultrasound. Oral Presentation. 14th International Symposium of Therapeutic Ultrasound, April 14, 2013. Las Vegas, NV.

Manuscripts:

Farr N, Wang YN, D'Andrea S, Lee DH, Hwang JH. MR-guided focused ultrasound induced hyperthermia for enhancing drug delivery in a pancreatic cancer mouse model. (*In preparation*)

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