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Program and Abstracts

Part 3: PSY-01 through VET-06
Oral Abstracts

Part 3 contains abstracts PSY-01 through VET-06.

The following abstracts were withdrawn by the authors:

BRT-41  END-03  NDG-08
BST-01  IMM-07  SDT-02
BST-07  MOV-10  URO-04

BRT-38 has been omitted as a duplicate of BRT-39, the latter having more complete author information.
Focused Ultrasound for Neuromodulation in the Treatment of Opioid Addiction

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Background: The opioid epidemic continues to be a public health crisis in the U.S. New data released from the Center for Disease Control and Prevention in May 2022 showed record-high drug overdoses, with more than 107,000 deaths in the last year, mainly due to the highly addictive synthetic opioid fentanyl added to many other illegally sold substances. The misuse of and addiction to opioids cause an economic burden in the US of more than $78.5 billion a year. While FUS has been applied to numerous clinical and preclinical applications, targeted neuronal suppression using FUS-mediated neuromodulation has not been evaluated for opioid addiction. Both mechanical (i.e. non-thermal) and the non-destructive thermal effects of FUS may transiently suppress neuronal activity. Therefore, we will evaluate both the thermal and nonthermal biophysical ultrasound mechanisms in our experimental model. Here, we will use low intensity focused ultrasound (LIFU) to suppress the neuronal activity in the nucleus accumbens (NAc) of a fentanyl-self administration rodent model, to study whether LIFU will lead to the diminution of drug-seeking behaviors. We will first optimize the LIFU parameters for suppressing NAc activity in rats (Aim 1). We will then evaluate the optimized LIFU treatment (NAc versus visual cortex active control region) for decreasing fentanyl self-administration in rats (Aim 2).

Materials and Methods: Aim 1: Optimization of LIFU treatment parameters and duration for suppression of the neuronal activity in the NAc of rats. These treatments will be performed on either a benchtop FUS device or a commercial small animal MRgFUS system (Image Guided Therapy or IGT, Pessac, Fr) to target the NAc (Figure 1). The IGT system operates at 1.5 MHz, fitted to a Bruker Biospec 7.4 Tesla MRI scanner. After optimization of the LIFU treatment parameters, we will perform LIFU before we inject fentanyl (0.04 mg/kg i.p.) to induce NAc neuronal activation. FUS treatments in the NAc will be carried out unilaterally; the contralateral NAc will serve as an internal sham control. The degree of FUS-mediated suppression of the fentanyl-induced neuronal activity will be examined by Fos immunohistochemistry (IHC). Labeled Fos-immunoreactive nuclei in four sections of both left and right hemispheres from each rat will be automatically counted using IPLab software. Since Fos expression is maximal at 2 hours after pharmacological injection, we will euthanize all rats 2 hours after fentanyl injections. Fentanyl will be injected into the rats 2h, 6h, 24h & 48 h post-FUS. For each of the 4 time points, we will treat one rat of each parameter group (mechanical and thermal effects). Relative levels of Fos will be used to demonstrate the degree of LIFU-induced suppression as a function of time post-FUS treatment.

Aim 2: Comparison of fentanyl self-administration versus food self-administration after LIFU. Rats will be implanted with jugular catheters and trained to self-administer fentanyl, during daily sessions (2.5 ?g/kg/i.v. infusion, 3 hrs/ day for 10 days), see Figure 2. We will first test the rats' baseline motivation to self-administer fentanyl with active lever presses as we progressively increase the number of presses required to get a fentanyl infusion.
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Progressive ratio (PR) schedule. Next, we will administer the optimized LIFU, targeting the NAc bilaterally or the visual cortices (active control) bilaterally, 14 animals/group x 2 groups (Figures 2C & 2D). We will also test the rats' post-LIFU motivation to self-administer fentanyl using the PR schedule of fentanyl reinforcement, once weekly for two weeks following LIFU treatment to examine the enduring effect of the single LIFU treatment (Figure 3). Since NAc lesions may impair the rats' ability to respond at high rates to receive food reinforcers, a control comparison group trained to self-administer natural food rewards will receive the same training and testing to examine the effects of LIFU-NAc or LIFU-visual cortex treatments on motivation for food reward (Figure 3).

Results: Since we are just initiating this project, we do not yet have results for the study. However, we expect to have some preliminary results by the time of the symposium.

Conclusions: To be presented at the symposium.

Acknowledgment/Funding Sources: Focused Ultrasound Foundation and a grant from the NIH (DP1DA053719-01, PI: L.Chang)

Figure 3 – Experimental Design to Evaluate Drug-Seeking Behavior of Fentanyl Administration after LIFU

Sprague Dawley rats (6 weeks old)
Males and females (n=56)
LV catheter surgery
N=28
Recovery 6-8 days

Progressive ratio (PR) schedule
Self-administration of fentanyl
2.5 μg/kg/intravenous infusion,
3 h/day for 10 days
LIFU to Visual cortex
N=14
LIFU to N. Accumbens
N=14

Progressive ratio (PR) schedule
Self-administration of food
N=28, 10 days
LIFU to N. Accumbens
N=14
LIFU to Visual cortex
N=14

Progressive ratio (PR) schedule
Self-administration of fentanyl
2.5 μg/kg/intravenous infusion,
3 h/day for 14 days
Euthanize and harvest brain for cFos IHC and validation of FUS treatment

Monitoring food reward for 14 days

Figure 3. Flowchart showing the steps involved and the animals in each group (fentanyl vs. food self-administration) and the subgroups (NAc vs. visual cortex).
Safety and Feasibility of Focused Ultrasound Neuromodulation for Substance Use Disorder

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Background: In 2021, drug overdose deaths were at the highest in recorded history. Despite advances in behavioral and pharmacological treatments, including medication for opioid use disorder such as buprenorphine, over 50% of those receiving treatment for OUD experience drug use recurrence (relapse) of opioid and/or other substances. Given the prevalence of OUD and other SUDs (many of which do not have medication treatments available), the high drug use recurrence rates, and the alarming increase in drug overdose deaths, novel treatment strategies are desperately needed. As such, we initiated an FDA approved clinical trial to assess the safety, tolerability, and feasibility of a Low Intensity Focused Ultrasound (LIFU) neuromodulation in participants with co-occurring SUDs (poly-SUD). Secondary aims included evaluating the impact of LIFU on substance craving.

Materials and Methods: Following eligibility determination, two male participants with a history of poly-SUD and who were enrolled in a comprehensive SUD treatment program, received sham LIFU followed by active LIFU sonication, applied bilaterally to the Nucleus Accumbens (NAc) at low power. Once safety and tolerability of this low power dose was confirmed in these first two participants following a ninety day follow-up, the FDA approved continued enrollment of two additional participants (one male and one female) with an "enhanced" dose of LIFU sonication. In addition to safety, outcomes included the acute assessment of substance craving using a cue reactivity paradigm prior to, during, and following LIFU sonication. Daily craving (non-cue induced) ratings, via a visual analog scale (VAS) where 0 = no craving and 10 = maximum craving, were also assessed in the days prior to and the week following LIFU sonication.

Results: LIFU applied to the NAc was found to be safe and well-tolerated both during sonication procedures and throughout the ninety-day follow-up assessment for participants who received both the lower and enhanced LIFU doses. Relative to sham sonication, enhanced NAc LIFU acutely attenuated self-reported craving for all substances including opioids, alcohol, and benzodiazepines. In addition, daily craving ratings were significantly reduced for several substances during the week following NAc LIFU relative to the days preceding sonication. Specifically, in the male participant, post-LIFU craving reductions were noted for heroin (4.2±0.5 vs. 1.8±0.5), alcohol (6.0±0.7 vs. 2.4±1.2), methamphetamine (3.2±0.4 vs. 0.0±0.0) and benzodiazepines (2.8±0.4 vs. 0.0±0.0) and, in the female participant, post-LIFU reductions were noted for alcohol (3.0±1.5 vs. 0.0±0.0) and nicotine (5.6±1.9 vs. 1.2±0.8) (all p’s <0.001). In addition, while the latter participants craving for other substances including methamphetamine, cocaine, and benzodiazepines was relatively low at baseline in the days prior to LIFU (~1-2 out of 10), she consistently rated these as zero in the week following LIFU.

Conclusions: In summary, in participants with poly-SUD, LIFU applied to the NAc was safe and well-tolerated, acutely reduced cue-induced substance craving during the LIFU sonication, and potentially reduced craving in the week following LIFU sonication. While promising, NAc LIFU requires further investigation in a controlled trial with a larger cohort of participants to establish safety, determination of optimal treatment parameters, and prolonged outcome measurement to further elucidate the impact of LIFU on substance craving and ultimately substance use and relapse.
Low Intensity Focused Ultrasound for Depression – Methods for a First-in-Human Study

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Background: Low intensity focused ultrasound (LIFU) is an emerging technology in neuropsychiatric research that can deliver reversible, non-invasive deep brain neuromodulation with millimeter precision. LIFU’s spatial precision and non-invasive nature sets it apart from current technologies such as transcranial magnetic stimulation, transcranial electrical stimulation, or deep brain stimulation. Furthermore, its reversible effects allow for the causal study of deep brain structures implicated in psychiatric illness. This presentation will describe safety and imaging outcomes from a controlled, first-in-human study using LIFU targeting the amygdala in depressed patients, with and without comorbid anxiety.

Materials and Methods: Study procedures are performed under FDA IDE G200146. After informed consent, four patients (one female, three male) with depression (ages 35-63) received MRI-guided LIFU (single transducer, fundamental frequency: 650 kHz; PRF: 10Hz; pulse-width: 5ms; 20 sonications, 30s on/off, ISPTA.3: 719 mW/cm²). This work is performed as part of an ongoing study. LIFU is delivered by targeting the amygdala or control region (primary somatosensory cortex; S1). LIFU administrations are separated by >1-week in a controlled, crossover design. Participants were assessed immediately after LIFU, and at 24-hours and 1-week. Safety assessments include clinical MRIs (prior to and following all LIFU, at 24 hours and 1-week post-LIFU), alongside regular psychiatric, neurologic, and neuropsychological evaluation. Functional MRI, including amygdala imaging and perfusion is assessed after each LIFU session.

Results: The study is currently ongoing; no serious adverse events have been observed to date. Anticipated results will evaluate the safety of LIFU administration across clinical MRI, neurological exams, neuropsychological testing, and psychiatric assessments. Neuroimaging analyses will compare the effects of LIFU to our targeted region (amygdala) compared to control (somatosensory cortex), and evaluate whether the state of the brain (i.e., task-based MRI) impacts any potential effects of LIFU.

Conclusions: This early first-in-human study is evaluating whether LIFU can safely and reversibly modulate the amygdala in patients with depression with and without comorbid anxiety. The trial is currently ongoing; no serious adverse events have been observed to date. With further study of neural effects and their relationship with clinical symptom change, LIFU may be a transformative technology in neuropsychiatric research and treatment.

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**In Vivo Fluorescein-Mediated Sonodynamic Treatment in an Intracranial Malignant Glioma Mouse Model: A Pilot Study**

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**Background:** High grade gliomas (HGGs) are the most common malignant primary brain tumors; they still have negative outcomes, despite therapeutical efforts in improving Progression Free Survival and Overall Survival. Among the new therapeutic strategies sonodynamic therapy (SDT) is emerging as an auspicious treatment. Fluorescein (FL) use instead of other sonosensitizers is applicable to brain tumors other than glioma. The aim of this pilot study is to evaluate for the first time SDT with fluorescein (FL) and low-intensity focused ultrasound feasibility and set-up in an intracranial mouse model, its potential to inhibit glioma growth and its influence on tumor microenvironment.

**Materials and Methods:** This study was conducted on 24 immune competent 6-week-old female C57BL6/N mice that received intracranial injections of 5x10⁴ GL261 murine glioma cells. We evaluated four conditions (6 mice per group): fluorescein; focused ultrasound (FUS); FL-SDT; control. Fluorescein dose intraperitoneally injected was 10mg/kg for both fluorescein-only and FL-SDT group. To perform FL-SDT, fluorescein was administered 20 minutes before sonication. FUS was performed using a single element planar transducer (0.485 Freq./MHz) with 10% duty cycle (350 cycles, 10ms period) for 20 minutes in FUS-only and FL-SDT group. Multiple 7T MRI scans were conducted exploiting T2 and gadolinium enhanced T1 sequences. First scan was conducted 7 days after inoculation to exclude complications as hemorrhages or hematomas. After treatments, macroscopical glioma growth or inhibition was assessed through 7T MRI at 14th, 21st and 28th day. Effects on tumor microenvironment, as lymphocyte recruitment and MDSCs infiltration were evaluated through flow-cytometry at 14th - 21st - 28th day. (Figure 1)

**Results:** In vivo 7T-MRI performed shows no treatment-related complications as hemorrhages or hematomas. 7T-MRI displays tumor growth inhibition in mouse from FL-SDT group, while it evidences tumor growth in fluorescein-only, FUS-only and control groups (figure 2). Through flow-cytometer analysis, brain tumor samples from C57BL6/N mice show maintained trend in increasing CD8+ infiltration and MDSCs reduction in FL-SDT treatment group, the opposite to findings from control group (figure 3-4). No influence was found on CD3+ CD4+ population. Analysis on mice treated only with fluorescein or only with FUS show mild influence on TME with inconsistent results.

**Conclusions:** Sonodynamic therapy with fluorescein and focused ultrasound is a feasible technique for in vivo treatment in a mouse model of deep-seated intracranial high-grade glioma. Moreover, our findings comprehend selective macroscopical tumor growth control obtained by FL-SDT, with interesting modification of tumoral microenvironment. Further studies engaging numerous cohorts are needed to statistically assess FL-SDT effectiveness and to clarify its mechanism of action.

**Acknowledgment/Funding Sources:** The present work was supported by Focused Ultrasound Foundation (Charlottesville, VA, USA), Acoustic NeuroImaging and Therapy Laboratory and Molecular Neuro-oncology Unit of IRCCS Istituto Carlo Besta.
Figure 2. 7T MRI follow up; T1 with gadolinium. (A) Control group, showing tumor growth at 21st day. (B) FUS-only group and (C) fluorescein-only group, showing tumor growth at 28th day. (D) FL-SDT group, showing no radiological evidence of glioma at 28th day.

Figure 3. Bar plots based on CD11b+ Gr1+ cell (MDSC) percentages in tumor harvests derived from flow-cytometry. Fluorescein-mediated SDT is the only group showing a trend in reducing MDSCs infiltration rate compared to Control group (p<0.005 vs. controls).

Figure 4. Bar plots based on CD8+ CD3+ cell percentages in tumor harvests derived from flow-cytometry. A slight non-significant infiltration of CD8+ T cells was detected at day 14, with a subsequent robust increase of their frequency (P<0.005 vs control).
Towards Preclinical Evaluation of Sonodynamic Therapy for Cerebral Cavernous Malformations

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Background: Cerebral cavernous malformations (CCM) are lesions in the brain's blood vessels that occasionally bleed and cause severe headaches or seizures. Here we used mouse models of the disease to test if incision-free surgery with focused ultrasound could slow down or reverse the progression of lesion formation and reduce bleeding in the brain.

Sonodynamic therapy (SDT) is a minimally invasive anticancer treatment strategy that relies on the use specific sonosensitizers, such as 5-aminolevulinic acid (5-ALA) or fluorescein. Following i.v. administration, these compounds accumulate in tumor tissue. Subsequent exposure to low-intensity focused ultrasound (FUS) leads to cytotoxic events such as release of reactive oxygen species (ROS), consequently ablating the target cells. Here we propose to adapt this approach for investigational treatment of CCM. It has been shown that the expansion of CCM can be driven by continuous recruitment of normal endothelial cells to the lesion by the mutant CCM cells, thereby inciting the growth of cavernomas. Therefore, selective ablation of mutant cells with SDT might halt further growth of these lesions.

Materials and Methods: We have established two mouse models of CCM using the conditional alleles of the Krit1 and Ccm2 genes. After genetic ablation of Krit1 or Ccm2 with the tamoxifen-inducible Pdgfb-CreER or Cdh5-CreER driver during the early postnatal development, CCM phenotype can be induced in these mice that closely resembles the human condition. We have optimized the timing of Krit1 ablation to postnatal day P5-P7, which improves survival and enables widespread development of CCM lesions throughout the adult mouse brain (Figure 1). Further, we have determined that these lesions are readily detectable with 7T MRI, particularly with T2-SPACE and SWI sequences, and confirmed that MRI data correlates with histology (Figure 2).

Results: In our initial experiments, we have used mouse crosses between Cdh5 CreER/+; Krit1 flox/+ males, and Krit1 flox/flox females. The newborns were induced with a subcutaneous injection of dilute tamoxifen at postnatal day P5. At 2 months of age, the animals harboring the correct genotypes were prescreened with T2 SPACE sequence in the Bruker ClinScan 7T MRI system. Sonication experiments are being optimized with LP-100, a newly acquired focused ultrasound system designed for clinical MR scanners. The first results have indicated satisfactory precision of MRI-guided FUS treatment, and evaluation of the efficiency of cell ablation, and collateral tissue damage is underway. In the next phase of this project, we will infuse sonosensitizers and apply FUS in the range of 0.1-0.2 MPa PNP to select lesions. The 5-ALA sonosensitizer, widely used in the clinic, will be tested, as well as BZL-100 (tozuleristide), which has shown a surprisingly high specificity for CCM lesions in angioma patients.

Conclusions: Our data paves the way towards the overarching goal to evaluate the potential of sonodynamic therapy for CCM. Our team is uniquely poised to address the feasibility of FUS mediated treatment strategy for CCM pathology.

Acknowledgment/Funding Sources: FUS Foundation seed grants
Preclinical Study the Potential of Sonosensitizer-Mediated Sonodynamic Therapy on Malignant Brain Tumor Treatment

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Background: Malignant glioma is a common and severe primary brain tumor, the prognosis is extremely poor with a median overall survival of approximately 1 year, and a relative very low survival rate at 5 and 10 years approximately (5% and 3%, respectively). Therefore, development for new treatment strategy is in urgent need. Recently, the potential of sonodynamic therapy (SDT) using sono-sensitive molecules such as 5-aminolevulinic acid and fluorescein to treat brain tumor is highly noted. In the present study, rodent ectopic brain tumor models were used to evaluate the treatment effect for SDT. These data will serve as references of clinical trial application to Taiwan FDA.

Materials and Methods: Rat C6 glioma cells were subcutaneously implanted to the hind flank of SD rats. In vivo cytotoxicity of 5-ALA / fluorescein assisted SDT were evaluated by the tumor size changes. The histological features of tumor specimen were investigated by hematoxylin & eosin, and apoptosis-specific staining to determine the pathological changes post SDT treatment.

Results: Both 5-ALA and fluorescein were used to test the SDT treatment effect. For 5-ALA assisted SDT, 180mg/kg 5-ALA were orally administered and treated with FUS (0.4MPa, duty10% for 20min). For fluorescein assisted SDT, 16mg/kg fluorescein were intraperitoneally administered and treated with FUS (0.35MPa, duty10% for 10min). The tumor growth rate of both SDT groups were significantly inhibited as compared with control groups.

Conclusions: In this study, we examined the effect of 5-ALA and fluorescein assisted SDT on subcutaneous C6/SD tumor model. Our study demonstrated that tumor growth rate was significantly inhibited, suggesting SDT is effect for noninvasive tumor treatment.

Acknowledgment/Funding Sources: The authors acknowledge to Focused Ultrasound Foundation for funding support.

Figure 1. Sonodynamic therapy treatment effect on subcutaneous C6 glioma. A: 5-ALA assisted SDT. B: Fluorescein assisted SDT. Data are depicted as fold change over baseline tumor volume at Day 1.
Sonodynamic Therapy for Metastatic Melanoma: An In Vivo Study

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Background: Brain metastases represent the most common malignant brain tumor in adults. Melanoma is one of the most common tumor types to metastasize to the brain. The application of focused ultrasound with a substance that sensitizes cells to the damaging effects of sound is called sonodynamic therapy (SDT). Previous research has demonstrated that the cytotoxicity of SDT in inhibiting tumor cell proliferation was based upon the generation of ROS or singlet oxygen, which mediated the upregulation of p53 and induction of tumor cell apoptosis. The ability to deliver highly focused ultrasound to brain targets through the intact skull has become feasible.

Materials and Methods: C57BL/6J mice (weight 19g; age~ 7 weeks, Charles River) were used. B16F10 was purchased from ATCC and maintained in RPMI-1640 supplemented with glutamine 500ml (Gibco, 11875-093), 25ml FBS + 7.5ml HEPES (1M, Gibco, REF 15630-080 100ml) + anti-anti in a humidified incubator at 37°C containing 5% CO₂. 5ALA was purchased from Sigma Aldrich.

Results: To generate the unilateral subcutaneous only tumor model, 2x10⁵ B16F10 cells were injected subcutaneously on the right flank. Initially, we tested the tumor growth curve in the subcutaneous melanoma mice model. Subsequently, 200mg/kg 5ALA was administered IP in each subcutaneous tumor-bearing mouse 4 hours prior to tumor harvesting. 405nm blue light flashlight was used to evaluate the fluorescence intensity of PpIX. Red color (emission wavelength is 635nm) was visualized in all 3 tumors harvested from melanoma-bearing mice. We used one mouse as a negative control, which only received the same amount of normal saline (200ul). One C6 glioma-bearing Wistar rat was used as a positive control. 400ul of 5ALA was administered IP. The homogenous red color was determined under the blue-light flashlight. The next step will be to treat subcutaneous melanoma-bearing mice with predetermined acoustic parameters in the presence of 5ALA.

Conclusions: The current preliminary study results demonstrated the success of uptake of 5ALA in mouse melanoma subcutaneous model in addition to the tumor growth information, which paves the way to the next phase of the present research.

Acknowledgment/Funding Sources: Funds from Focused Ultrasound Foundation

Figure 1. growth curve of subcutaneous B16F10 in C57BL/6J mouse
Pioneering Focused Ultrasound Blood-Brain Barrier Opening for Drug Delivery to Cerebral Cavernous Malformations

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Background: Cerebral cavernous malformations (CCMs) are hemorrhagic lesions in the central nervous system that affect approximately 1 in every 200 people. Lesions largely increase in size and hemorrhagic risk over time, inducing severely disabling symptoms to patients. Current treatments are highly-invasive and/or minimally effective. Minimal effectiveness of some therapeutics in vivo demonstrates the need for increased local dose to lesions. Blood-brain barrier opening (BBBO) with magnetic resonance-guided focused ultrasound (MRgFUS) offers a non-invasive and effective strategy for meeting this need. Further, BBBO via MRgFUS opens the possibility for larger molecular weight biologics to be leveraged for CCM treatment, an avenue currently unexplored due to physical barriers against transport of these large molecules. Thus, our goal for this study was to (i) demonstrate safe and effective BBBO to the CCM microenvironment and (ii) develop protocols for delivery of biologics to the CCM microenvironment.

Materials and Methods: CCMs were induced in mice by postnatal, endothelial-specific (Pdgfb1CreER or Cdh5CreER) Krit1 ablation. MRI protocols (T2-SPACE and susceptibility-weighted imaging [SWI]) were optimized at 7T MRI to monitor CCMs prior to and following FUS BBBO. Selected cavernomas were sonicated (i.v. microbubbles; 1.1-MHz; 10-ms bursts; 0.5-Hz PRF; 2-min duration) at either 0.2-, 0.3-, or 0.4-MPa peak-negative pressure. Delivery of gadolinium contrast agent (Gd-BOPTA, MultiHance), gadolinium-conjugated albumin (Galbumin, BioPal), or gadolinium-conjugated IgG (Gd-IgG, BioPal) will be assessed by the fold contrast enhancement of the sonicated region in the MR image following FUS compared to the pre-sonication image.

Results: FUS-mediated BBBO delivered gadolinium contrast agent to the CCM microenvironment at 0.2-, 0.3-, and 0.4-MPa as a function of peak-negative pressure (Fig. 1A-B). SWI pre- and post-treatment revealed no increases in iron deposition, indicating lack of hemorrhage and thus safe BBBO parameters (Fig. 1D). The pattern of contrast enhancement suggests that access to the CCM microenvironment is via the perilesional microvasculature rather than the lesion itself (Fig. 1A, C). We expect that peak-negative pressures of 0.3 MPa or higher will be necessary for sufficient delivery of larger biologics (i.e. gadolinium-conjugated albumin and IgG).

Conclusions: Current treatments for CCM are invasive, and promising pharmacologic candidates lose their effectiveness in vivo. MRgFUS offers a non-invasive, effective strategy for increasing local dose to lesions and for unlocking new therapeutic options such as antibody and gene therapies. Our work demonstrates the first-ever FUS application for CCM, laying the foundation for the much-needed improvement of therapeutic options for this debilitating disease.

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Figure 1. Focused Ultrasound Blood-Brain Barrier Opening of the Cerebral Cavernous Malformation Microenvironment Can Be Safe and Effective for Drug Delivery.
Inflammatory and Cellular Damage Markers in a Pig Model of Intraventricular Hemorrhage with and without MRgHIFU Treatment

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Background: Intraventricular hemorrhage (IVH) occurs when blood vessels in the brain rupture, which can lead to bleeding within the ventricles. Inflammation resulting from the hemorrhage has been implicated in the pathogenesis of post-hemorrhagic hydrocephalus. Magnetic-resonance image-guided high-intensity focused ultrasound (MRgHIFU) is a technique where magnetic resonance imaging (MRI) is used to locate and monitor the tissues where high-intensity focused ultrasound (HIFU) therapy is being applied. This could be used in IVH to break up blood clots that form from blood in the ventricles. A study using a model of chronic IVH was published recently by Lai et al (2021) where brain tissue samples (sections) were collected from pigs treated with MRgHIFU and processed for histology. Examining the brain sections using immunohistochemistry provides insight into the inflammatory processes resulting from IVH and how MRgHIFU affects this process.

Materials and Methods: A pig model was used to simulate IVH in vivo, with the pigs usually living around 4 weeks after the blood infusion. The pigs from Lai et al (2021) had been perfusion-fixed after the experiment to prevent decay. 4um coronal brain slices were taken from both control and experimental pigs. The primary antibodies used were mouse anti-pig GFAP (Glial Fibrillar Acidic Protein) and Caspase-3, and rabbit anti-pig CD11b monoclonal antibodies. Horse-Radish Peroxidase (HRP) and Diaminobenzidine (DAB) were used to label the antigens. A Zeiss AxioZoom light microscope was used to take zoomed in images along the ventricular walls using the 2.3 objective and 11.2 zoom for 25.76 magnification. Exposure times were set at 380 ms for each image. QuPath was used to calculate the percentage of cells positively stained with the antigens.

Results: Results show that the pigs showed higher GFAP, CD11b, and Caspase-3 staining along the ventricle walls, indicating potential astrogliosis, apoptosis, and leukocyte infiltration. Quantifying the staining using percentage of cells stained, calculated using QuPath, revealed higher amounts of positive cells in the treated pigs for GFAP and CD11b staining, and in the untreated pigs for Caspase-3 staining, but these results were not statistically significant.

Conclusions: Further research into how HIFU affects inflammation, astrogliosis, and apoptosis is recommended. It is recommended that these studies use a larger sample size, both in terms of number of pigs as well as how many areas of the brain they sample from, to get a more comprehensive picture. If such results are replicated, then determining ways to mitigate astrogliosis during HIFU treatment is essential.

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Figure 1.
Figure 2. GFAP Histology

Figure 3. Caspase-3 Histology

Figure 4. CD11b Histology
Behavioral and MRI Analysis of Focused Ultrasound Neuromodulation on the Kainic-Acid-Induced Epilepsy Models

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Background: Focused ultrasound (FUS) has been confirmed to be able to enhance neuroprotection and inhibit the epileptic signal. With this mimic temporal lobe epileptic syndromes to clinical features, the purpose of this study is to confirm whether FUS modulates epileptic behavior during chronic phase in a chronic epileptic small animal model.

Materials and Methods: Nineteen Sprague-Dawley rats were separated to 3 groups: group 1 (n = 6) served as non-KA control, group 2 (n = 7) received KA intra-amygdala injection to be served as KA-only positive control (Fig. 1(A)), and group 3 (n = 6) received KA intra-amygdala injection and received twice FUS exposure (frequency = 500 kHz, ISPTA = 0.5W/cm², multiple exposures at week 9 and 14) in chronic phase of the KA-induced epilepsy (Fig. 1(B)). The injected KA toxic effect was observed via longitudinally followed T2-weighted MR images with the change of hippocampal and striatum volume change was quantitated. Several behavioral tests have been conducted: the open field test was conducted for evaluating exploring and anxiety; the cylinder test was conduct for evaluating the of limb function; the social test was conduct for evaluating socialization and water maze test was applied for evaluating memory.

Results: Animals received KA were found the hippocampal volumes in the KA-injected hemisphere were significantly shrunk (Fig. 2(A)) (-14% in KA models compared to non-KA group; p < 0.05). However, in KA+FUS animals, hippocampal volume changes in KA-injection hemisphere gradually increased to 2.69 ± 17.82% after twice FUS treatments (p < 0.05 compared to KA-only group) (Fig. 2(B)). The KA model was also found with presenting anxiety than non-KA animals in general. FUS exposure slightly increased the exploring in KA+FUS group when compared to the KA-only group (p < 0.05, compared to non-KA group) (Fig. 3(A)). The social analysis showed that multiple FUS treatments improved sociability in KA+FUS group as that in non-KA animals (Fig. 3(B)). The cylinder test showed that KA significantly decreased usage of left paw, but FUS exposure significantly increased the usage comparing with pre-FUS period (Fig. 3(C)). The water maze evaluation showed that FUS treatment retarded the memory impairment. The Whishaw’s error decreased in KA-only groups (declining to 82.18 ± 16.7%) during 15-20 weeks and was significantly different to non-KA animals. KA+FUS group slightly decreased to 87.53 ± 9.08% by multiple FUS treatment (Fig. 3(D)).

Conclusions: This study supported that the structural hippocampal damage due to KA injection can be rescued with multiple FUS exposures, and matched behavioral improvement. The results support the neuroprotection effect of multiple FUS treatment in the KA-induced small animal model, and might have rehabilitation potential to clinical epilepsy.
Figure 2. Comparison of the hippocampus volume in MRI among the testing group. The Pre-FUS, Post-1st FUS and Post-2nd FUS are denoted as I1, I2, I3.

Figure 3. Behavioral task analysis. (A) Open field test. (B) Social test. (C) Cylinder test and (D) Water Maze test.
Investigation of Microbubble Response to Short Burst Phase Keying Ultrasound Exposures for Blood-Spinal Cord Barrier Opening

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Background: The blood-spinal cord barrier (BSCB) greatly hinders therapies for spinal cord tumours, injury and diseases. Focused ultrasound (FUS) mediated by microbubbles (MBs) has shown pre-clinical success with non-invasive BSCB opening in both small and large animal models. To address the challenge of standing wave formation in the spinal canal, a novel Short Burst Phase Keying (SBPK) pulse scheme was previously developed. Recent in vivo work has demonstrated no significant difference in MRI enhancement post MB-mediated FUS between 2ms and 10ms SBPK pulses, observing a drop off of acoustic emissions associated with MB activity after 2ms (Fletcher et al 2021). This study aims to closely investigate the response of MBs to SBPK pulses and determine if modulated pulses can prolong the persistence of stable MB cavitation.

Materials and Methods: A MB-flow phantom (tube inner diameter = 0.5mm, flow rate = 5µL/s) with dual-aperture FUS (frequency = 514kHz, 50mm diameter, focal number = 1.2) tested the acoustic response of Definity MBs to modified SBPK treatments (30s, 1s pulse repetition frequency, 12ms pulse length) over 15 fixed pressures (0.1MPa-1.5MPa). The effect of varying burst repetition period (BRP, 30µs, 60µs, 120µs), burst shape (original SBPK, Hanning windowed SBPK) and phase keying (SBPK, non-phase keyed short bursts) were investigated in comparison to the control of original 60µs BRP SBPK. Analysis of acoustic emissions collected by the receiver (frequency = 250kHz) involved short time windowing, pulse inversion when applicable, separation into individual sonications, Fourier Analysis, and indexing of harmonic maximum projections. MB activity was further visualized in phantoms (2.5% agarose, 100µm and 50µm diameter channels) with a single transducer setup using fast-frame optical imaging (10k frames per second).

Results: Acoustic emissions analysis revealed that increasing BRP does not appear to prolong stable MB cavitation, specifically the persistence of 2nd harmonics signals across 12ms pulses. 60µs BRP SBPK reached the greatest 2nd harmonics however with steep signal drop off at 2ms for 0.8MPa and higher. Comparable magnitudes of 2nd harmonic signals are observed throughout 12ms pulses of shorter 30µs BRP SBPK but with greater levels of associated broadband emissions. At relevant pressures for observing peak MB activity (1.0-1.2 MPa), Hanning windowed SBPK on average reached maximum subharmonic signals 45 ± 7% greater and 2nd harmonic signals 39 ± 6% lower than original SBPK. Non-phase keyed short bursts presented peaks of 2nd harmonic activity within 12ms pulses up to 3 times as long as SBPK at relevant pressures. However, non-phase keyed short bursts only presented marginal increases in signal magnitude as pressure ramped. Initial optical imaging results confirm the utility of the 50µm channel phantoms for close observation of MB flow and activity.

Conclusions: Preliminary acoustic results suggest the efficacy of SBPK in comparison with non-phase keyed bursts showing minimal MB activity. However, tests utilizing pulse inversion are needed to lower noise for non-phase shifted bursts. Further studies correlating both acoustic and optical measurements will help clarify ideal BRP and burst shape for optimal MB response.

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High Intensity Focused Ultrasound Induced Lesion Assessment Using Multi-Frequency Single Transducer Harmonic Motion-Derived Displacements

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Background: High intensity focused ultrasound (HIFU)-induced thermal ablation is gaining popularity for treating tumors due to its low cost and repeatability. A successful ablation procedure depends on the sufficient ablation margin covering the targeted tumor volume. While ultrasound imaging is typically used to guide ablation procedures, it suffers low echogenicity changes and attenuation due to the presence of gas bubbles during ablation. Instead of ultrasound-based morphologic features, an assessment of mechanical properties can better delineate lesion areas because thermal ablation alters the mechanical properties of tissue. Toward the goal of accurately assessing lesion size, this study uses single transducer-harmonic motion imaging (ST-HMI) with a multi-frequency excitation pulse to generate displacement images of the HIFU-induced lesion at an oscillation frequency of 100-1000 Hz in a single acquisition. ST-HMI modulates the discrete excitation pulse (DEP) duration to generate amplitude modulated acoustic radiation force and interleaves the tracking pulses with DEPs to estimate displacement.

Materials and Methods: The feasibility of ST-HMI to delineate lesions is performed by HIFU-induced ablation of chicken muscles ex vivo (N=2). HIFU ablation is performed by a single-element 4-MHz FUS transducer (Sonic Concepts, Inc, Bothell, WA, USA) with an amplitude modulation frequency of 50 Hz and peak positive pressure of 22 MPa. The focal spot (1 versus 2) and duration (2 min versus 4 min) were varied to change the formed lesion size. After ablation, ST-HMI with multi-frequency excitation pulse was performed using a Verasonics Vantage ultrasound system and L7-4 linear array imaging transducer (Philips Healthcare, Andover, MA, USA) with excitation and tracking pulse center frequency of 4 and 6 MHz. HIFU ablation and ST-HMI planes were co-registered by placing highly reflecting metallic pins for the planning phase. B-mode and ST-HMI-derived peak-to-peak displacement (P2PD) images at 100-1000 Hz were generated to compare the lesion size and delineation due to the two different HIFU parameters. The performance of P2PD images at different oscillation frequencies was compared in terms of contrast.

Results: Fig. 1 shows a photograph, B-mode, and ST-HMI-derived P2PD images at 100-1000 Hz when lesions were formed with (focal spot #, duration) of (2, 4 min, panel A) versus (1, 2 min, panel B). Note that all P2PD images at 100-1000 Hz were generated in a single acquisition. Focal spot #2 and duration #4 min induced a larger lesion than focal spot #1 and duration #2 min which is evident in both photographed and ST-HMI displacement images. B-mode was unable properly delineate the ablated area. While ST-HMI P2PD images at all frequencies were able to delineate the lesion, the highest contrast (C in Fig. 1) was achieved at 400 Hz and 900 Hz for larger versus smaller lesions which indicates that higher ST-HMI frequency is better for delineating smaller lesions and vice versa. The maximum P2PD ratio of the lesion over non-lesion region, achieved at 400 Hz and 900 Hz, was 4.1 and 2.3 for the lesion in panel A versus B which suggests that HIFU parameters in panel A generated a stiffer lesion than in panel B.

Conclusions: This initial feasibility shows that ST-HMI can map different size HIFU-induced lesions by collecting P2PD images at 100-1000 Hz in a single acquisition. Future studies will develop an algorithm to automatically calculate the lesion area from P2PD images at 100-1000 Hz, compare ST-HMI-derived lesion area with histopathological findings, and apply ST-HMI for monitoring HIFU-induced ablation of tumors.

Acknowledgment/Funding Sources: This work was supported by the NIH under Grant R01 CA228275.

Figure 1. See next page.
Fig. 1: Photograph, B-mode ultrasound, and normalized peak-to-peak displacement (NP2PD) images of high intensity focused ultrasound (HIFU)-induced lesions in chicken muscles ex vivo with 4 min duration and 2 focal spots (A) versus 2 min duration and single focal spot (B). Oscillation frequency and corresponding contrast (C) were given on the title of each NP2PD image. NP2PD delineated HIFU-induced lesion (magenta contour) than conventional B-mode image. The performance of different frequencies varies with HIFU parameters which indicates that frequency can be exploited to better delineate the lesion. The green dashed rectangle represents the best performing frequency for each panel. Blue and red contours represent the region of interest in lesion and non-lesion regions, respectively for the contrast calculation. There is a slight mismatch between photography versus ultrasound/displacement image due to the difference in the plane.
Focused Ultrasound-Induced Cavitation Renders Cancer Cells Susceptible to Radiation Therapy, Hyperthermia

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Background: Focused ultrasound (FUS) has become an important non-invasive therapy for solid tumor ablation via thermal effects. The cavitation effect induced by FUS is applied for histotripsy, support drug delivery and the induction of blood vessel destruction for cancer therapy. Numerous studies reported that cavitation-induced sonoporation could provoke multiple anti-proliferative effects on cancer cells. Therefore, the combination of FUS-induced cavitation and other treatment modalities like radiation therapy (RT) or hyperthermia (HT) is of great interest but research in this field is inadequate. In our study, effects of FUS-induced cavitation to RT, standard HT were investigated comprehensively at the cellular in human prostate cancer (PC-3) in vitro.

Materials and Methods: A special high-throughput FUS system was used for cancer cell treatment with a customized 1.467 MHz single focused transducer. Characterization of acoustic behavior of gas-filled cavities was performed via a fiber-optic hydrophone (FOH) system and chemical terephthalic acid method helped to define the acoustic parameters, which could lead to occurrence of cavitation at the bottom of 96-well cell culture plates where cancer cells were located. Cells were treated firstly with FUS with cavitation (FUS-Cav, 1136 W/cm²) for 40 s, followed by 10 Gy X-ray irradiation (RT) or water bath HT (45 °C for 30 min). Clonogenic assay was performed to examine the long-term survival of clonogenic cells after different treatment regimes. Cell viability and invasiveness were evaluated using WST-1 assay and Transwell-Matrigel assay. Pore formation in cell membrane (Sonoporation) was detected with fluorescence staining by Propidium Iodide (PI) and Cell Mask Stain during sonication.

Results: 1. Cavitation occurs at and above the acoustic intensity of 344 W/ cm² for the 1.467 MHz transducer. 2. FUS-Cav demonstrates significant long-term additive effects to RT or HT at the cellular level showing a 32-fold/2-fold reduction of prostate cancer cell clonogenic survival fraction in combination treatment (FUS-Cav + RT / FUS-Cav + HT) compared to single treatment (RT/HT) respectively. 3. FUS-Cav can also significantly increase the sensitivity of prostate cancer cells to RT or HT by decreasing short-term cell potential to invade and metabolic activity: the relative cell invasion of prostate cancer cell PC-3 was reduced to 33.35 ± 0.60 % (FUS-Cav + RT) and 42.67 ± 1.17 % (FUS-Cav + HT) in comparison to single treatment (RT: 52.82 ± 1.31 % / HT: 70.73 ± 2.14 %). Compared to relative cell metabolic activity after single treatment (RT: 81.53 ± 4.62 % / HT: 78.79 ± 5.89 %), the combination of FUS-Cav and RT/HT led to a significant loss of metabolic activity to 46.51 ± 3.61 % (FUS-Cav + RT) and 62.98 ± 4.74 % (FUS-Cav + HT). 4. The most significant numbers of PI-stained cell nuclei were observed in the group of FUS-Cav.
Conclusions: Our findings demonstrate short-term and long-term additive effects of FUS (short FUS with cavitation) to RT or HT at the cellular level are reducing cell invasion, metabolic activity and clonogenic survival. Our results suggest that FUS induced cavitation may increase the effects of RT and HT by interrupting cell membranes of the prostate cancer cells, with the potential to be a promising adjuvant therapy in prostate cancer treatment.

Acknowledgment/Funding Sources: SONO-RAY project from the Federal Ministry of Education and Research

Figure 2. FUS-Cav supports RT and HT reducing PC-3 cell clonogenic survival and invasion. Representative photographs of colony formation (A) and invaded cells (B) after different treatment, scale bar = 100 µm

Figure 3. FUS-Cav induced sonoporation in PC-3 cells. Representative fluorescence microscopy images for PC-3 cells showing an increase in red PI fluorescence during FUS-Cav, scale bar = 30 µm
Non-contrast MR Biomarker of Thermal Ablation in MRgFUS Treatments via Supervised Learning to MR-Registered Histology

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Background: An ongoing challenge for clinical translation of MR-guided FUS is measuring non-viable tissue after treatment to ensure negative margins. Current clinical MR metrics of thermal necrosis, non-perfused volume (NPV) acquired acutely after ablation and cumulative thermal dose of 240 °C@43°C (CEM240), have variable accuracy when compared to histological outcomes. Additionally, gadolinium contrast prevents re-treatment and can lead to toxicity. Therefore, there is strong motivation for a non-contrast multiparametric MR (MPMR) predictor for acute assessment of MRgFUS ablations.

Materials and Methods: VX2 tumor cells (1x10⁶) were injected into the quadriceps muscle of n=4 New Zealand white rabbits and grown to ~2 cm in length. Tumors were partially ablated using a custom MRgFUS system consisting of a 256-element phased-array transducer (Imasonic; 10-cm focal length, 14.4×9.8 cm aperture, 940 kHz) and single-loop imaging coil, inside a 3T PrismaFIT scanner (Siemens). Multi-point thermal ablation sonications were performed in each rabbit (9-14 30-s sonications, 45-60 acoustic W), monitored with real-time PRF MR temperature imaging (MRTI; 3D segmented-EPI; ¬Tacq=4.5 s; 1.5×1.5×2 mm). MPMR images (T2-weighted images and ADC maps (b=20, 500)) were acquired immediately pre- and post-ablation. Acute CE-T1w images were acquired after post-MPMR imaging and NPV was expertly segmented. Each subject was re-imaged in the same position 3 days later, then euthanized and the quadriceps was harvested for H&E staining. Treatment and day 3 follow-up MR images were longitudinally registered via intensity-based elastic deformation as previously described.¹ All MR images were elastically registered to serially sectioned, digitally scanned, and 3D-reconstructed H&E as previously described.² H&E was expertly segmented to generate a labeled dataset for training two voxel-wise supervised classifiers of tissue necrosis: a) logistic regression classifier (LRC, Scikit-Learn v0.23, L2 penalty) and b) random forests classifier (RFC, Scikit-Learn v0.23, maximum depth=21, 700 estimators). Classifier inputs were a) cumulative thermal dose (CTD) from MRTI and post-pre-ablation differences in b) T2w and c) ADC. Training data comprised of quadriceps voxels in n=3 subject, and test data comprised of the 4th subject. This was repeated for all n=4 subjects. Classifier performance was reported in each subject and compared to clinical metric predictions of thermal necrosis.

Results: ROC and AUC (area-under-the-curve) results for each subject are shown in Figure 2. Acute NPV had the greatest mean AUC (AUC=0.860), while the CTD model had the lowest (AUC=0.727). AUC scores for the MPMR LRC and RFC models were lower than acute NPV on average (AUC=0.818 and 0.778), but they outperformed CTD. The Dice scores of models and clinical metrics were computed in the test data in each subject (Figure 3). Mean Dice for LRC and RFC models, (Dice=0.644, 0.530 respectively) was greater than CTD and CEM240 (Dice = 0.446, 0.432 respectively). Optimization of the CTD model did not improve Dice over the 240 CEM240 prediction. However, the addition of T2w and ADC data in the MPMR LRC model improved Dice significantly over CEM240 (p=0.0554) and CTD (p=0.0185). The LRC model Dice

Figure 1. Representative cross-sections of volumetric MPMR classifier and clinical metric predictions of thermal necrosis in the rabbit quadriceps of each subject. Filled pink region denotes the registered histological label of thermal necrosis.

Figure 2. ROC and AUC (area-under-the-curve) results for each subject are shown in Figure 2. Acute NPV had the greatest mean AUC (AUC=0.860), while the CTD model had the lowest (AUC=0.727). AUC scores for the MPMR LRC and RFC models were lower than acute NPV on average (AUC=0.818 and 0.778), but they outperformed CTD. The Dice scores of models and clinical metrics were computed in the test data in each subject (Figure 3). Mean Dice for LRC and RFC models, (Dice=0.644, 0.530 respectively) was greater than CTD and CEM240 (Dice = 0.446, 0.432 respectively). Optimization of the CTD model did not improve Dice over the 240 CEM240 prediction. However, the addition of T2w and ADC data in the MPMR LRC model improved Dice significantly over CEM240 (p=0.0554) and CTD (p=0.0185). The LRC model Dice
score was similar to acute NPV (Dice = 0.675). Precision, Recall and Dice scores for each model and clinical metric are shown in Figure 3.

**Conclusions:** MR innate contrasts such as relaxation times and diffusion can detect acute tissue changes immediately following thermal ablation such as edema, membrane permeability, and thermal coagulation. In this study, a simple logistic classifier was trained with MPMR data to develop an acute, non-contrast imaging biomarker for thermal necrosis. The MPMR classifier outperformed both the clinical CEM240 prediction and the optimized CTD model, and performed comparably to the acute NPV. Further improvements in quantitative imaging and incorporation of nonlinear classification models may result in a highly accurate acute, non-contrast method for assessing MRgFUS thermal ablations in tumors.

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Identification of the HIFU Focus Using 3D Passive Acoustic Mapping with a Rotational 2D Linear Array Probe

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Background: The high-intensity focused ultrasound (HIFU) technique delivers acoustic energy to a designated area and concentrates it into a localized region known as the focal zone. Intense scattering signals are generated from the focal spot. In ultrasound-guided therapy, passive acoustic mapping (PAM1D) has been utilized to monitor acoustic sources or scatters of medium with a 1-dimension (1D) linear probe, which is confocally aligned with a HIFU transducer (Fig. 1a). However, the conventional method has a structural limitation of a 1D linear array that can only monitor the fixed 2-dimensional (2D) imaging plane. Suppose the focal spot forms out of the imaging plane due to the inhomogeneity of the propagation medium. In that case, the assumption of radiofrequency (RF) signals scattered in the geometric focal zone are no longer valid. In the present study, by visualizing the acoustic field, we demonstrated the feasibility of a 3D PAM using a rotational 2D probe (3D-PAMr2D). That monitors the HIFU focal spot. The r2D probe was implemented by a mechanically rotating 1D linear array probe. We compared three PAMs reconstructed by a 1D, 2D, and r2D ultrasonic probe.

Materials and Methods: A full 3D numerical simulation was conducted to establish a 3D-PAM model (Fig. 1). The simulation utilized a spherically focused single-element HIFU transducer to act as an acoustic source traversing a heterogeneous medium. The HIFU transducer has a geometric focus of 45 mm, an aperture diameter of 62 mm, and a disk with a radius of 21 mm cutout to enable coaxial alignment of a 1D linear array probe. The HIFU transducer was driven with a driving frequency of 1.5 MHz and 5 cycles. For RF acquisition, a 1D linear array probe with 128 elements and a pitch of 0.2 mm was modeled, and elements ranging from 0 to 39 and from 88 to 127 were selected at every 10° rotational angle from 0° to 179° with respect to the center of the probe to cover the cylindrical volume of interest (Fig. 1b). After the HIFU pulse was triggered, the 1D linear array probe obtained RF signals scattered from the medium for 90 µs. Then the rotation angle of the 1D linear array probe was changed before triggering the next HIFU pulse. The rotational axis of the 1D linear array probe was shared with the central axis of the HIFU transducer so that the central axis of the whole system remained constant for all subsequent changes in the angle. A time-domain-based "Delay-and-Sum" (tDAS) was applied throughout multiple elements at various angles to reconstruct the 2D or 3D PAMs. We validated the performance by comparing (a) a 3D simulated beam pattern (ground truth) to the PAMs reconstructed by (b) a conventional 1D linear array, (c) a 2D array, (d) a rotational 2D array (proposed method) (Fig. 2).

Results: Fig. 2a shows the X-Z and Y-Z planes of the 3D acoustic beam pattern as the ground truth. Conventional PAM visualized the X-Z imaging plane only due to its structural nature. In contrast, the 3D PAM was constructed by applying the tDAS algorithm with RF signals received from 1360 virtual elements created by mechanically rotating 80 out of 128 elements (Fig. 1). PAM2D or PAMr2D could visualize the scattering map on an imaging plane at an arbitrary angle. It enables the 3D monitoring of acoustic field, which was not feasible previously with conventional PAM1D. The resolution of the 3D PAM was set to 0.2
The image resolution can be refined by decreasing the size of the grid and increasing the number of the grid. However, enhancing image resolution requires an increase in computation time.

**Conclusions:** In therapeutic ultrasound applications, passive acoustic mapping techniques are accepted as supplementary monitoring algorithms. We successfully implemented a disk-shaped rotational 2D array by rotating a 1D linear array probe to construct 3D PAM in the numerical simulation. We expect that the proposed method has the potential to monitor the actual focal spot formed in 3D space by overlaying it on top of a 2D or 3D B-mode image in a clinical ultrasound machine. Further research on a scanning algorithm and element arrangement is suggested to optimize scanning, computation time, and accuracy.

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**Figure 2.** Simulation results of the beam pattern and passive acoustic mappings. (a) the ground truth beam pattern of the HIFU generated by the numerical simulation, (b) a conventional PAM1D, (c) PAM2D, (d) PAMr2D.
Design and Evaluation of a CMUT Array Prototype for Transcranial Ultrasound System

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Background: Transcranial focused ultrasound (tFUS) in combination with microbubbles (MBs) holds great potential for targeted drug delivery in the brain. As this technology advances to the clinic, the requirement for highly sensitive and broadband detection of microbubble dynamics to ensure safe and effective treatments is becoming more stringent. Current tFUS systems use piezoelectric transducers which are limited in bandwidth and don't provide flexibility in terms of receive sensitivity because of difficulties in integration with electronics. Capacitive micromachined ultrasonic transducers (CMUTs) are micro-electromechanical system (MEMS) based structures and have been shown to provide higher receive sensitivity and broader bandwidth, making them an excellent transducer for MB detection (Kilinc et al. IUS, 2021). Different from piezoelectric transducers, CMUTs have two main operation modes, conventional and collapse modes, that can be controlled by bias voltage. Meanwhile, the conventional mode has lower frequency response, the collapse mode has higher frequency response, increased receive sensitivity, and large bandwidth. Therefore, beyond their enormous potential as receivers, depending on the applied bias voltage, CMUTs can be utilized as transmitters in tFUS applications. In this work, we evaluated a small-scale tFUS system based on CMUT arrays for dual-mode operation for MB-mediated BBB permeabilization.

Materials and Methods: In this study, a commercial CMUT array (CM5 from Philips Engineering Solutions) was used. As shown in Fig. 1, the CM5 has 64 elements with a 12 x 21 mm active aperture area. The CMUT array was characterized to determine its operating regime by adjusting bias voltage. A hydrophone (HGL-1000 from Onda Corporation) was used to characterize the beam profile of a single CM5 array and the generated Peak Negative Pressure (PNP) was measured for conventional and collapse mode. Based on these results, a small-scale tFUS system consisting of six CM5 arrays and geometrically focusing at 5 cm was designed and evaluated using Field II simulations to determine focusing and adequate pressure level generation for BBB opening application. The simulated transducer configuration was subsequently modeled on computer-aided design (CAD) software and a water-tight frame was printed on a 3D printer. CMUT arrays and electronic boards were then integrated into the frame. Fig. 2 shows the picture of the setup with a hydrophone to map 2-D acoustic fields and to measure pressure around the focal region. The transducers are driven with power amplifiers and the input phases are adjusted based on hydrophone measurements.

Results: The conventional mode center frequency of CM5 is measured at ~0.5 MHz while it has a ~2.5 MHz operation center frequency in collapse mode (Fig. 3). In single CMUT measurements, PNP values up to 80 kPa were obtained at ~5 cm distance with 60 V AC in conventional mode at 500 kHz which is suitable for human studies. The same single array can generate 150 kPa PNP in collapse mode at 1 MHz, suitable for animal studies. PNP values of ~300 kPa and ~600 kPa were measured at 0.5 MHz and 1 MHz respectively using only the six arrays in the array which are suitable for MB excitation in BBB applications. The field scans at 0.5 MHz and 1 MHz demonstrate the focusing capability.
of the array with a beam size of 1 mm × 2.5 mm and 0.5 mm × 1 mm for 0.5 MHz and 1 MHz, respectively shown in Fig. 4. These results demonstrate that the same CMUT array can generate sufficient levels for tFUS in a broad frequency range. The grating lobes apparent in the experimental measurements are due to large flat transducer arrays. They can be improved substantially by dividing each CMUT array into subarrays and applying appropriate phase delays to generate the desired curvature.

Conclusions: We have designed and validated a small-scale tFUS system based on six CMUT arrays. We demonstrated that our system can generate sufficient pressure at 0.5 MHz and 1 MHz for MB excitation. Combined with broadband (0.5-5MHz) and highly sensitive detection of MB activity and imaging of skull surface in the collapsed mode and considering larger number of CMUT arrays create unique opportunities for the development of novel dual-mode clinical-scale systems for tFUS.

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Figure 3. The frequency spectrum of the CM5 CMUT in conventional (black) and collapse mode (blue).

Figure 4. Normalized 2-D plane (lateral vs elevation directions) beam profile of the arrays at a) 0.5 and b) 1 MHz. The focal pressure values at c) 0.5 MHz and d) 1 MHz.
Focused Ultrasound (FUS) Treatment of a Spheroid In Vitro Tumour Model with a New FUS Applicator

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Background: FUS offers potential as an adjuvant therapy in cancer treatment. Therefore, analysis of FUS effects on cancer cells is necessary. We performed studies on two human cancer cell line spheroids using a newly developed high-throughput in vitro FUS applicator with 32 individual transducers. This study aimed to perform basic experiments with a new in vitro FUS device on a 3D tumour model to acquire insight into the effects of FUS at the cellular level. These experiments may contribute to a better understanding and predictions of cancer treatment efficacy.

Materials and Methods: For assessment of the 32 transducers performance of the new in vitro applicator (Fig. 1b), sound field measurements were performed in a water tank. The generated acoustic signals were acquired by a calibrated hydrophone (Type S, RP Acoustics) and analyzed offline using Matlab (The MathWorks). Human prostate cancer cell line PC-3 was grown in RPMI 1640 Medium (Thermo Fisher Scientific) and human glioblastoma cell line U87 was cultured in DMEM (Thermo Fisher Scientific). Spheroids were formed with an overlay formation technique in ultra-low attachment (ULA) 96-well CELLSTAR® round-bottom plates (Greiner Bio-One GmbH). The cells were cultivated for four days in a humidified incubator (Fig. 1). For FUS treatment, spheroids were transferred to US penetrable 96-well ?clear plates (Greiner Bio-One GmbH). Sonication parameters for 90 s: 1. ISPTA=2.95 W/cm²; signal repetition: 5 Hz (20 ms), duty cycle: 10%; and 2. ISPTA=5.9 W/cm²; signal repetition: 5 Hz (20 ms), duty cycle: 10%. After sonication, spheroids were transferred to corresponding wells of the U-bottom plate. Spheroids were analyzed for morphological changes with microscope, cell viability with ATP assay (CellTiter-Glo® 3D Reagent (Promega GmbH) and DNA damage using flow cytometry and γH2A.X assay (Cell Signaling Technology).

Results: The obtained 2D and 1D pressure distribution fields show the Peak to Peak pressure (Fig. 2). The 76 dB focal widths in the x- and y-directions are 1.4 mm and 5.5 mm, respectively. This is below the pitch of the well plate, confirming that there is little influence on individual wells by neighboring transducers. Microscopy of spheroids showed decomposition of the PC-3 spheroids immediately after FUS treatment at 5.9 W/cm². Interestingly, the spheroid reassembles 48 h post-treatment. In contrast, the U87 spheroids had a more tightened spheroid structure but with a reduction in spheroid area to 246,387 µm². U87 showed a higher sensitivity with a statistically significant loss in ATP metabolism after treatment at 5.9 W/cm² to 1.61 ± 2.45% (48 h) and 0.70 ± 0.94% (96 h) (Fig. 3). Flow cytometer analysis of dissociated PC-3 spheroids revealed a significant increase of fluorescence intensity (p < 0.05) 24 h post-treatment.
with FUS at an intensity of ~5.9 W/cm² to ~22% compared to untreated ~17%.

**Conclusions:** It was demonstrated that low-intensity FUS reduces spheroid growth, metabolic activity, and increased DNA double-strand breaks as well as cell-cell connections as seen in spherical cell cultures. The results suggest that cancer cell spheroids are more suitable for evaluation of FUS effects and will be further investigated.

Acknowledgment/Funding Sources: This research was funded by the German Federal Ministry of Education and Research (BMBF) under grant no. 03Z1L511 (SONO-RAY project).

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**Figure 2.** Assessment of the single-transducer pressure distribution in 2D and 1D. (a) and (b) show two 2D sound fields (Peak-to-Peak pressure in dB is plotted) acquired in a water tank measurement to assess the extent of the focal area. (c) Shows a lateral cross-section.

**Figure 3.** FUS reduced spheroid size and diminished spheroid metabolic activity. (a/b) Representative microscopy images of FUS-treated spheroids; the corresponding 3D reconstructions were obtained using ReViSP. PC-3 cancer cell line: Scale bar = 200 μm. U87 cancer cell line.
MRI-Compatibility Study for Combination of FUS and Radiation – a Experimental Rodent Study

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Background: Focused ultrasound (FUS) can be used to physiologically change or destroy tissue in a non-invasive way. A few commercial systems have clinical approval (CE Mark and/or FDA) for thermal ablation of solid tumors, for the treatment of neurological diseases, and for palliative pain management of bone metastases. The thermal effects of FUS are known to lead to various biological effects, such as inhibition of DNA damage, reduction of tumor hypoxia and induction of apoptosis. In our previous study, FUS-induced moderate heating in a temperature range of 40 – 47 °C has shown to sensitize tumor cells to radiation therapy (RT) in vitro. Here, we studied the MRI-compatibility of a developed matrix-array FUS transducer for radiosensitization as a combination therapy of FUS and RT in a xenograft mouse model.

Materials and Methods: A novel MR-conditional preclinical FUS phased array transducer consisting of an 11x11 elements matrix array probe with an aperture size of 10x10 mm and a frequency of 960 kHz was developed together with Fraunhofer IBMT (St. Ingbert) (Fig. 1A). To test its MRI-compatibility, MR images were obtained in 7T MRI (Bruker) with a gradient echo (FLASH) sequence (Parameters: TE = 15 ms; TR = 400 ms; slice thickness = 3 mm; FOV = 4x4 cm; matrix = 256×256; flip angle = 30°; no. of averages = 1) and spin echo (RARE) sequence was run with the same geometry except TE = 20 ms, TR = 800 ms. Xenograft tumor baring 7-15 weeks old male NMRI Foxn1nu/nu mice (Janvier Labs) were produced by subcutaneous injection of human prostate cancer cell line PC-3. Animals were treated with new FUS system in the 7T MRI at 4.8 W/cm2 to reach ~45°C and hold for 30 min. Temperature was controlled via fiber optics and proton resonance frequency shift (PRF) MR thermometry in parallel. In combination group, animals were treated with FUS followed by X-ray at single dose of 10 Gy in small animal radiation research platform (XStrahl). Effects of FUS and RT were assessed via hematoxylin-eosin (H&E) staining. Tumor proliferation was detected by immunohistochemistry of Ki67 and apoptosis was measured by TUNEL assay.

Results: The comparison of the MR image quality in the 7 T preclinical MRI with and without the transducer showed reduced SNR in presence of the transducer. A field-drift of 0.0443 % was observed when the transducer was sonicating. Without the transducer, the SNR was 157.17 when using the FLASH sequence (Fig. 2). Measurements on identical geometry with the presence of the transducer resulted in images with a SNR of 66.29. An inhibition of tumor growth by 4.6 times was observed in vivo in the FUS+RT group (85.29%) in contrast to the tumor volume of 393% in untreated control. At 40 days follow up, the impact of RT on cancer cells was significantly improved by FUS demonstrated by a reduction of cell nucleoli from 189 to 237 compared to RT alone. The tumor proliferation was reduced from 74.1% (control) to...
59.4 % (RT) and 7.9 % (FUS+RT) while apoptosis was enhanced 3.7-fold in FUS+RT group compared to single RT (Fig. 3). The result of H&E staining showed that single FUS treatment has limited effect on xenograft tumor and healthy organs.

**Conclusions:** Our results demonstrated that the matrix-array FUS transducer is compatible and safe to be used in a 7 T small animal set-up. Furthermore, the feasibility of combined MRI-guided FUS and RT for the treatment of heterotopic prostate cancer in a xenograft mouse model was shown and may provide a chance for less invasive cancer therapy through radiosensitization in the future.

**Acknowledgment/Funding Sources:** BMBF project 3MP-FUS (grant no. 13GW0619A)

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**Figure 2.** Measured mean signal-to-noise ratio profiles in 7 T of FLASH and RARE sequence of the phantom. (A) FLASH sequences show consistent values across all 13 slices. (B) RARE sequences show inconsistent image homogeneity.

**Figure 3.** The tumor growth of PC-3 xenografts was suppressed by FUS+RT treatment showing a decreased trend in tumor volume after treatment compared to RT alone (A). The prostate cancer xenograft tumor showed suppressed proliferation (Ki67, B) and enhanced apoptosis [Caption exceded character limit.]
Porous Silicon Nanoparticles and Microbubbles as Enhancers of MR-HIFU Therapy

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Background: Non-invasiveness of MR-guided high-intensity focused ultrasound treatment (MR-HIFU) makes it an attractive alternative when choosing between treatment methods for tumors. The problem with MR-HIFU treatment is that in some cases, sufficient thermal dose necessary for necrotization of target tissue cannot be achieved. This may be due to high tissue perfusion or heat conduction. Use of microbubbles as an enhancer of HIFU has already yielded better treatment outcomes.¹,²

Materials and Methods: This study investigated the effect of porous silicon (PSi) nanoparticles and microbubbles on the absorption of acoustic energy of ultrasound in MR-HIFU treatment, and what kind of effect absorbant concentrations have. Porous silicon nanoparticles and microbubbles contain gases that are expected to increase the absorption of ultrasound energy and increase the interaction between sound waves and microscopic gas bubbles i.e., cavitation. In that case, porous silicon nanoparticles and microbubbles could be used as an enhancer by making thermal effect of HIFU stronger and thus increasing the thermal dose. In this study following PSi nanoparticles were used: thermally hydrocarbonized with acetylene at 520 °C (THCPSi) that have short hydrocarbon species on the surface making it hydrophobic, thermally carbonized at 820 °C (TCPSi) which are covered with hydrogen free non-stoichiometric SiC layer making it hydrophilic, and thermally hydrosilylated with aliphatic 1-decene (DecPSi) which are hydrophobic. Both THCPSi and TCPSi particles have porosity of ca. 60%. DecPSi has initially the same structure as THCPSi and TCPSi, but is chemically re-etched making it highly porous (≥80%) with a hierarchical pore structure. The microbubbles were commercially available SonoVue microbubbles, having a phospholipid shell and loaded with sulfur hexafluoride gas (SF₆).

Results: In the experimental study, the samples were injected to a fantom and were sonicated using clinical MR-HIFU system. We found that THCPSi and DecPSi nanoparticles, as well as microbubbles enhance the ultrasound energy absorption. Of these three, the DecPSi nanoparticles were superior. Their enhancing effect on the temperature rise induced by plain MR-HIFU was more than 60% even at a low concentration of 0.25 mg/ml. The effect increased up to 250% as the nanoparticle concentration was increased to 4.0 mg/ml, which was 5 times higher than with microbubbles.

Conclusions: Based on this study, PSi nanoparticles and microbubbles have a potential to be useful as enhancers in MR-HIFU treatments.

References
A Conformable Skin-Cooling System for Body Magnetic Resonance Guided Focused Ultrasound Treatments

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Background: Ablation of large tumors routinely requires dozens to hundreds of individual sonications, repeatedly exposing the skin in the near- and far-field to low-level ultrasound intensities. This slow, regular exposure can cause heat to accumulate, leading to skin damage. MRgFUS devices utilize an inter-sonication delay period between successive sonications in an attempt to mitigate the risk of skin-burns. For large tumors that may require in excess of one hundred sonications, this cooling requirement can extend the total treatment time by multiple hours. This work describes the design and evaluation of a forced convection cooling device that actively cools the skin cooling during MRgFUS treatment without compromising ablation effectiveness or introducing artifacts into MR temperature monitoring.

Materials and Methods: The system consists of three main components (Fig. 1): (i) a component cart designed to be sited outside the MRI room, that houses the chiller, supply and return pumps, a water reservoir and an inline degassing system; (ii) a skin-cooling pad assembly that includes a welded pad with flow baffles, supply tubes and shunt valves; and (iii) a control box that is positioned adjacent to the MRgFUS control computer and contains the pressure controller, emergency stop switch, system alarms and pump power switches. The skin cooling system was evaluated under several conditions. Conformability to different anatomies was evaluated in a healthy human volunteer to demonstrate how placement and acoustic coupling could be achieved in the targeting of different targets. Through-transmission testing was performed to quantify effects of the skin cooling system on the ultrasound beam. A phantom study was performed to quantify the effects on MR thermometry precision. Finally, in vivo effects of the skin cooling system were evaluated in a porcine model by performing sonications 5 and 10mm from the skin surface under control and skin cooling conditions. Ablation depth was evaluated from MR temperature-based thermal dose measurements and gross pathology.

Results: The presence of the skin-cooling pad assembly in the near field of the ultrasound beam path does not cause any beam distortion or positional change, however, a 5 to 12% reduction of peak pressure was observed when comparing to the water only condition. The skin-cooling pad in an active flow condition did not cause any artifact or additional noise in the MR temperature imaging. The temperature precision in the flow off and on conditions was 0.048 and 0.054°C, respectively with no impact on image quality as well. Skin-cooling pad assembly conformability and acoustic coupling quality was confirmed in four potential anatomical targets. In all cases, the pad was able to conform to the anatomy with no bubbles present between the pad and skin (Fig. 2). The porcine studies demonstrated the use of the skin-cooling pad allowed for thermal dose to be deposited close to the skin.

Figure 1. Main components of the skin cooling system including (a) pumps, degasser and water reservoir, (b) a control box that contains feedback control electronics and all power switches and (c) the skin-cooling pillow assembly.

Figure 2. T1-weighted images showing good conformability and coupling to human anatomy at (a) knee, (b) shoulder, (c) abdomen and (d) lower buttock.
with a reduction of skin burn severity and size (Fig. 3).

**Conclusions:** A validated conformable, convective skin-cooling device is described that can be integrated with existing MRgFUS body systems to effectively prevent skin burns and potentially reduce lengthy treatment times. Design plans, parts lists and schematics for this system are available at https://github.com/fuslab-uofu/SkinCoolingDevice. This device is currently utilized clinically in desmoid tumor and uterine fibroid MRgFUS treatments.

Acknowledgment/Funding Sources: This research was funded by the FUS Foundation.

![Figure 3. Comparison of control and skin-cooling conditions in animal 2. Cumulative thermal dose is overlaid on an axial T2-weighted image obtained at the end of the sonication period. Sonication matrices are labeled for both the (a) control and (b) skin-cooling conditions.](image)

![Figure 4. Gross assessment of the porcine skin immediately post experiment. Any burns or other marks were noted for animals (a) 1, (b) 2 and (c) 3 (yellow arrows). The control side is shown in the top image with the skin-cooling side are shown in the bottom image.](image)
The Effects of Elastic Modulus and Impurities on the Distribution of Bubble Nuclei Available for Acoustic Cavitation in Polyacrylamide Hydrogels

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Background: Over the last decades, acoustic cavitation has been extensively studied in water with cavitation inception or bubble nucleation categorized as homogeneous or heterogeneous. However, the distribution of bubble nuclei available for acoustic cavitation remains relatively unexplored in biological tissues. In this study, the effects of elastic modulus and impurities on the distribution of bubble nuclei available for acoustic cavitation were evaluated in tissue-mimicking polyacrylamide hydrogels.

Materials and Methods: PA hydrogels were fabricated according to Lafon et al. (2005) with acrylamide concentrations of 17.5%, 20% and 22.5% v/v and 1% bovine serum albumin (BSA) (n=3 each). Hydrogel elastic modulus was calculated from speed of sound measured by 1.1 MHz contact transducers and density (mass/volume) of the hydrogels. A 1.5 MHz single element focused ultrasound transducer with f#=0.7 was used to induce cavitation in the hydrogels using 10-ms pulses with pressures ranging up from p-= 18 to 31 MPa and -6 dB focal dimensions of 9.4x1.2 mm (p-). Spatial distributions of the acoustic cavitation bubbles were observed at 0.075 ms using high speed photography at the frame rate of 40,000 fps. Captured images were binarized and overlaid to observe consistency of bubble nuclei available for acoustic cavitation in hydrogels exposed to focused ultrasound (n=3). Then, impurities of 0.25% w/v cholesterol crystals, 0.25% w/v calcium phosphate crystals (maximum dimension = 0.6 mm and 0.4 mm respectively) or BSA at 5% or 10% (maximum dimension 140 Å) were added in separate 17.5% v/v PA hydrogels (n=3 each). These gels were exposed to the same 1.5 MHz focused ultrasound and peak negative pressure was increased until cavitation was observed at 0.075 ms. Cavitation thresholds, defined as the peak negative pressure when cavitation probability reached 50%, were calculated.

Results: Created polyacrylamide hydrogels had elastic moduli of E=2.55, 2.62, and 2.67 GPa for 17.5%, 20%, and 22.5% v/v acrylamide respectively. For hydrogels of all elastic moduli, acoustic cavitation occurred at random locations within the -6 dB transducer focal volume when p-=18 MPa (Fig. 1a). Increasing the pressure to p-=31 MPa increased the bubble nuclei available for cavitation and caused shock scattering, which increased bubble location consistency for the 2.55 GPa hydrogel (Fig. 1b). However, increasing gel elastic modulus to 2.67 GPa decreased bubble nucleation and thus shock scattering induced bubble overlap for the same p-=31 MPa (Fig. 1c). Adding calcium phosphate crystals, cholesterol crystals, 5% or 10% BSA as impurities decreased acoustic cavitation threshold from approximately p-=13 MPa for 17.5% v/v hydrogels to approximately p-=11 MPa, p-=7 MPa, p-=9 and p-=7 MPa, respectively (Fig 2).

Conclusions: These results suggest that the distribution of bubble nuclei available for acoustic cavitation is random for polyacrylamide hydrogels of all elastic moduli. Further, it suggests that what constitutes a bubble nucleus for acoustic cavitation increases with peak negative pressure and decreases with elastic modulus. The addition of impurities to the hydrogels decreases the cavitation threshold, with hydrophobic cholesterol crystals showing a lower cavitation threshold than calcium phosphate crystals. Moreover, inhomogeneities on the size of proteins are sufficient to reduce the cavitation threshold. These results suggest both bulk tissue properties and structures as small as proteins may influence the location and

Fig. 1: Binarized high-speed images (n=3 each) overlaid for polyacrylamide elastic moduli A. 2.55 GPa gels exposed to peak negative pressure, p-=18 MPa shows no bubble overlap, B. 2.55 GPa gels exposed to p-=31 MPa shows shock scattering induced bubble overlap, C. 2.67 GPa gels exposed to p-=31 MPa shows decrease in shock scattering induced bubble overlap.
distribution of bubble nuclei available for acoustic cavitation. Future work includes similar evaluations of acoustic cavitation in cells and tissues.

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Fig. 2: Cavitation threshold measured for (a) 0.25% w/v calcium phosphate crystals (b) 0.25% w/v cholesterol crystals (c) 5% w/v bovine serum albumin (BSA) and (d) 10% w/v BSA embedded in 17.5% v/v polyacrylamide hydrogels (n=5 each)
Characterizing Shear Stress in Soft Tissue during HIFU Sonications Using Finite Element Modelling

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Background: High-intensity focused ultrasound (HIFU) is becoming a standard therapeutic tool in the clinic and is currently approved for multiple indications. The acoustic pressure used in HIFU therapy is significantly above the acoustic pressure used in diagnostic imaging. This acoustic pressure is a potential source for shear stress generation and propagation in soft tissues. Since soft tissues are comprised of a soft matrix, these shear stresses could be associated with specific biological effects such as the shearing of cell membranes causing transduction, mechanosensitive pathways, and gene activation. Herein, a novel finite element model (FEM) is developed to systematically assess the shear stresses generated in the vicinity of a focal zone of a HIFU beam.

Materials and Methods: HIFU sonification of 2D axisymmetric soft tissue is simulated in ABAQUS explicit (version 6.9, Dassault Systèmes SE, France). The non-linear material response of the soft tissue is modelled using neo-Hookean constitutive behaviour. The material properties for the soft tissue in the model are the density of 1050 kg/m³, shear modulus of 3000 Pa, and bulk modulus of 2.15 GPa. A single-element, concave-shaped HIFU transducer with an outer aperture diameter of 33 mm and focal length of 63.2 mm is used to produce acoustic waves in the simulations. A 5-cycle longitudinal wave along the Z-axis is produced with apodization at 500 kHz (fundamental) and 1.5 MHz (3rd harmonic), with a surface pressure of either 1 MPa, 5 MPa, or 10 MPa per frequency. After sonication, waves were allowed to propagate and focus, creating acoustic radiation force (ARF). The measurement of ARF is done for 10 ms. To avoid reflections from the boundary, the same material with added damping property is used. The smallest mesh element size is taken as 50 microns. Measurements are made at 2 mm, 6 mm, and 10 mm along the axis normal to the wave propagation, and shear stress and local displacement were measured along the Z-direction.

Results: Our simulations demonstrate propagation of the acoustic waves through the neo-Hookean material, focusing at 63 mm depth at 1540 m/s (Fig 1A) for a 1.5 MHz transmit frequency and 5 MPa surface acoustic pressure. The spatial distribution of shear stress at different time intervals shows a propagating shear wave along the radial direction (Fig. 1B). Measurement of the displacements along the z-axis at three different locations reveals different natures of the shear waves for 500 kHz and 1.5 MHz (Fig. 2). For 500 kHz, the displacement field shows persistent oscillations as opposed to that in 1.5 MHz, where a single pulse of displacement is seen. This difference could be attributed to resonant oscillations since the natural frequency of the material is close to 500 kHz. The difference between the peak displacements for 500 kHz and 1.5 MHz also hints toward the role of resonance. This difference between the two transmit frequencies is also reflected in the measurements of the shear stress (Fig. 3). The time to peak for the shear stress at three locations does not demonstrate any dependence on transducer operating conditions (Fig. 4B), implying a fixed shear wave speed of 1.67 m/s. However, the effect of transmit frequency on peak shear stress shows a pressure-dependent behaviour. We speculate that this decrease in the peak shear stress at a higher transmit frequency is due to the mechanical resonance in the tissue.

Figure 1. A. Longitudinal acoustic wave propagation in hyperelastic, neo-Hookean material for transmitting frequency of 1.5 MHz, 5 MPa surface pressure. B. Subsequent shear wave propagation after the longitudinal waves reached focal zone.
Conclusions: In conclusion, the shear wave speed is calculated from time to peak and time of flight approaches and closely agrees with the theoretical speed observed in soft tissue. The speed and peak shear stress were slightly higher in the case of 500 kHz transmit frequency. The higher shear stress could be attributed to large displacement occurring at the node. Also, with increased surface pressure, the peak shear stress increases. We expect this modelling approach to help better understand the role of transverse wave propagation in HIFU applications.

Figure 2. A. Displacement is measured at 2, 6 and 10mm from focal zone for sonication at 500kHz. B. Displacement is measured at 2, 6 and 10mm from focal zone for sonication at 1.5MHz. The peak displacement reduces as the distance increases from the focal zone.

Figure 3. A. Shear stress is measured at 2, 6 and 10mm from the focal zone for sonication at 500kHz. B. Shear stress is measured at 2, 6 and 10mm from focal zone for sonication at 1.5MHz. Shear stress magnitudes were significantly different for frequencies.

[Figure 4 was omitted from abstract submission.]

Figure 4. A. Peak shear stress values at radial distances of 2, 6, and 10mm from the focal zone. Peak shear stress is higher for 500kHz than that for 1.5MHz. B. The time to peak for displacement is calculated to demonstrate speed of shear wave propagation.
Noninvasive, imaged-guided, focused ultrasound neuromodulation for the control of hyperglycemia in a swine model

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Background: Post-operative hyperglycemia from insulin resistance is an extremely common condition that increases morbidity and mortality, and has not been adequately addressed with intensive insulin therapy. Vagus nerve stimulation (VNS), a common neuromodulation therapy, could be used to lower glucose levels and increase insulin sensitivity, but it has surgery related complications and also produces undesired effects, such as bradycardia and symptoms from the airways. Glucose-sensing neurons have been found in the vessels of the porta hepatis (PH) and superior mesenteric artery plexus (SMA), and non-invasive FUS of peripheral glucose-sensing neurons at the PH could suppress hyperglycemia in rodents with acute inflammation. However, the translational significance of these findings in rodents is unclear. This study is to validate its safety and effectiveness in an anatomically and physiologically realistic swine model. To optimize noninvasive, image-guided sub-organ noninvasive FUS to maximally increase insulin sensitivity, FUS will be targeted at PH and/or SMA with doses. Our long-term goal is to use noninvasive, sub-organ level FUS for treating both acute and chronic disorders characterized by insulin resistance, including type 2 diabetes.

Materials and Methods: The effect of FUS on insulin sensitivity is assessed by the hyperinsulinemic-euglycemic clamp (HEC) protocol. To quantify insulin sensitivity independently of the glucose level, the HEC was used with a constant insulin infusion rate (0.5mU/kg/min). HEC equilibrium will be achieved through adjusting the glucose infusion rate (GIR) every 7 min based on the measurement of glucose level in the blood. When the coefficient of variation (CV) of blood glucose levels is less than 10% for at least 30 min, HEC will be considered a successful clamp. Then, the animals receive FUS, and the GIR is adjusted to bring the glucose level to the equilibrium level in the following 90 minutes after FUS. The effect of FUS on insulin sensitivity was calculated from the changes in GIR from the baseline level. The FUS system allows for both ultrasound imaging and therapy through the same co-registered probe after customization from LOGIQ-E10 (by GE Healthcare). It can output a maximum intensity of 3321W/cm² (pulse width of 200us, frequency of 2.27MHz). A total of 10 adult pigs (45Kg, Yucatan) were used in the study. The HEC were done under general anesthesia. After placement of I.V line for insulin and glucose infusion and femoral arterial line for blood sampling, HEC was achieved by adjusting the GIR. FUS was delivered at different organs (PH vs SMA) and doses (55% full power vs sham; time: 5min vs 30min). When the same animal used in multiple survival experiments, a minimum of 5 days between two procedures was allowed to recover. 3 healthy animals used to decide which area is used for FUS, we tested the acute effect of FUS by stimulating PH, SMA, and both areas for 30minute. Then we tested the effect of FUS for the treatment of post-operative hyperglycemia in 7 surgically stressed animals (4 FUS and 3 sham). All experiments were approved by the IACUC of the Feinstein Institute.

Results: 30 minutes of FUS at 55% of maximum intensity causes GIR to increase bigger when FUS targets at SMA than at PH. While there was a similar effect when FUS stimulated...
at SAM alone or at both SMA and PH. We then used the FUS stimulated at the SMA for 30min in surgically stressed animals. We found that there was hyperglycemia after surgery. Out of our expectation, FUS treatment increased the hyperglycemia more than sham control animals.

**Conclusions:** 30 minutes of FUS at 55% of maximum intensity targeted at SMAplexus has a stronger effect than at PH; Surgical stress induced post-operative hyperglycemia; Out of our expectation animals after FUS showed severer post-operative hyperglycemia than sham-treated animals. As the limited number of animals, additional experiments were needed to confirm the observation.

**Acknowledgment/Funding Sources:** Supported by Focused Ultrasound Foundation.

**Figure 2.** FUS on insulin sensitivity from stimulation with high power (55%) at PH (30min), SMA (30min), and PH (30min) + SMA (30min).

**Figure 3.** Effect of sham FUS. A), blood glucose level during HEC and sham FUS; B), GIR during HEC and sham FUS; C), blood glucose level change in two days.

**Figure 4.** Effect of FUS. A), blood glucose level during HEC and FUS; B), GIR during HEC and FUS; C), blood glucose level change in two days.
Radiosensitization Effect of Magnetic Resonance Imaging-Guided Focused Ultrasound in Xenograft Prostate Cancer Model

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**Background:** Focused ultrasound (FUS) has been approved for clinical ablation of uterine fibroids, prostate cancer and essential tremor under magnetic resonance (MR) imaging guidance. Mild hyperthermia induced by FUS was reported to change tissues physically and support other treatment modalities like radiation therapy (RT) or chemotherapy in a non-invasive way. In our previous study, FUS-induced hyperthermia (FUS-HT) at the temperature range of 40 - 47 °C has shown sensitization effect to RT in vitro. Here, we investigated the radiosensitization effect of FUS-RT in a xenograft prostate cancer mouse model using a newly developed MR-compatible FUS system.

**Materials and Methods:** A novel preclinical FUS system developed together with Fraunhofer IBMT comprising an MR-compatible phased-array transducer (2 MHz) with 11x11 elements and was installed in a 7T preclinical MRI (Bruker, Pharmascan 7 T). The xenograft prostate cancer model was established by subcutaneous injection of PC-3 cells in nude mice on the right flank. FUS-HT treatment was performed at ~ 4.8W/cm² to reach 45°C and hold for 30min. The real-time temperature during treatment was controlled via fiber optics (Luxtron) and MR-thermometry in parallel. RT was performed at a single-dose of 10Gy using the small animal radiation research platform (XStrahl Medical) followed by FUS within 1h. Effects of FUS and RT were assessed via hematoxylin-eosin (H&E) staining. Tumor proliferation was detected by immunohistochemistry of Ki67 (Thermo Fisher) and apoptosis was measured by TUNEL assay (Sigma-Aldrich).

**Results:** The impact of RT was significantly enhanced by FUS showing a reduction of tumor nucleoli number to 189 compared to RT alone (237 nucleoli). Suppression of tumor growth was observed in FUS+RT group demonstrating a 4.6-fold decrease in tumor volume compared to untreated control. The tumor proliferation was reduced from 74.1% (control) to 59.4% (RT) and 7.9% (FUS+RT) while apoptosis was enhanced 3.7-fold in FUS+RT group compared to single RT. The results of H&E staining showed that single FUS treatment has limited effect on xenograft tumor and healthy organs.

**Conclusions:** The newly developed FUS system showed compatibility in a 7 T MRI system for safe small animal applications. Our in vivo results demonstrated the additive effects of combined MRI-guided FUS and RT for the treatment of prostate cancer in a xenograft mouse model compared to RT alone. The combination of MRI-guided FUS and RT may provide a chance for less invasive cancer therapy through radiosensitization.

Acknowledgment/Funding Sources: SONO-RAY project from the Federal Ministry of Education and Research.
Effects of Prostatic Calcifications on MRI-Guided High-Intensity Directional Ultrasound Ablation

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Background: As with diagnostic ultrasound, large calcifications can hinder therapeutic ultrasound leading to sub-optimal thermal dose delivery to the intended ablation zone. When small calcifications (>3 mm) are identified in men seeking MRI-guided transurethral ultrasound ablation (TULSA), susceptibility-weighted MRI (SWI) can be used intraprocedurally to guide the positioning of therapeutic ultrasound elements with respect to calcifications. We assess the impact of small calcifications on ablation coverage benchmarked against a previously-published FDA registration study.

Materials and Methods: Pre-TULSA screening for calcifications was performed with CT for 17 men; mean (range) slice thickness was 1.6 (0.6-5.0) mm. In nine men, intraprocedural SWI (1.0mm slices) was used to guide the positioning of therapeutic ultrasound elements with respect to calcifications. Calcification in-plane and through-plane diameters were measured on CT and SWI, and their impact on ablation coverage was assessed using MRI thermometry. Maximum temperature and thermal dose maps from MRI thermometry were segmented in 90-degree quadrants across the active ultrasound elements, with presence of calcification assessed based on SWI and phase images. Impact of calcifications on radial temperature profile was assessed based on the location and magnitude of peak temperature from the center of ultrasound element to the edge of the intended ablation zone.

Results: 25 calcifications were identified across 17 patients. All calcifications identified on CT were visible on SWI. In 4 patients, SWI phase images were used to differentiate calcifications from hemosiderin deposits. Mean (range) diameter was 3.8 (1.4-10.4) mm on CT and 4.0 (2.2-10.8) mm using SWI. SWI diameters were larger by median 22% in at least one dimension for all patients and in 42/50 measurements overall. With SWI-guided device placement in 9 men, median (IQR) proportion of target volume reaching boiling temperature was 4.0 (2-8.0) % and 3.0 (0-7.0) % in sectors with and without calcifications based on MR thermometry from TULSA treatment. Adequate thermal dose was achieved in men with and without calcifications: 98 (93-100) % vs 98 (95-100) %. In the FDA registration study, which did not have SWI-guided device placement, 93% (90-98) % of quadrants with calcifications reached adequate thermal coverage compared to 98 (93-100) % overall, and 6 (1-9) % with calcifications had target volume approaching boiling vs 0 (0-5) % overall. While median periurethral temperature (6 mm from edge of ultrasound element) was higher in quadrants with calcifications: 79 (74-82) °C vs 66 (65-72) °C, total thermal dose per quadrant was higher when calcifications were not present: 6E13 (6E12-3E20) CEM43 vs 10E19 (10E18-10E19) CEM43, which is related to longer re-sweeping time in quadrants with no calcifications where index lesion was typically located: 7 (0-22) min/quadrant vs 9 (7-10) min/quadrant. When SWI was not used for device placement, quadrants with calcifications also experienced higher periurethral temperature (77 (72-78) °C vs 65 (64-68) °C); however, longer re-sweeping times were observed (4 (0-7) min/quadrant vs 3 (1-4) min/quadrant) which led to a higher amount of thermal dose deposited near ultrasound applicator: 8E19 (1E17-2E21) CEM43 vs 4E19 (2E19-8E32) CEM43. Radial peak temperature was higher when calcifications were present: 87 (76-93) °C vs 76 (67-96) °C and typical location of peak temperature was unchanged: 8 (8-12) mm vs 8 (8-10) mm. In the FDA registration study, peak temperature was also higher in quadrants with calcifications (84 (73-95) °C vs 78 (67-89) °C) but located closer to ultrasound applicator: 8 (6-10) mm vs 10 (8-12) mm.

Conclusions: Intraprocedural SWI detected all CT-identified calcifications, tending to overestimate the diameter but guiding effective device positioning. Use of intraprocedural SWI was associated with adequate thermal dose achieved in the intended ablation zone.
Figure 1. Appearance of calcification on screening CT and intraprocedural SWI. Phase images used to differentiate between calcification and hemosiderin deposit on Siemens MRI.

Figure 2. Intraprocedural SWI used to position a 2.5 mm long calcification between two ultrasound elements.

despite the presence of small calcifications. CT remains the gold standard for pre-TULSA calcification screening, and further studies are warranted to optimize SWI protocols, correlate the size of calcifications on CT and SWI, and predict their impact on ablation coverage.

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Pivotal Study of Transurethral Ultrasound Ablation of the Prostate: MR Thermometry Parameters and Clinical Response at 4-Year Follow-Up

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Background: Prostate cancer (PCa) is the second most commonly diagnosed cancer in men and one of the leading causes of mortality. Active surveillance or radical therapy comprise the standard of care for patients with early-stage PCa. Radical therapy is associated with the risk of long-term sexual, urinary, and rectal toxicity, while active surveillance carries risk of disease progression. Magnetic resonance imaging (MRI)-guided transurethral ultrasound ablation (TULSA) is a noninvasive method of thermal coagulation with real time MR guidance and thermometry. The 2021 multi-center pivotal TACT Study (NCT02766543) reported excellent three year clinical outcomes. Here we assess real-time MR-thermometry (MR-t) parameters in relation to clinical outcomes.

Materials and Methods: Of 115 TACT study patients, a subset of 9 were treated at our institution with whole-gland TULSA. The protocol included biopsy-confirmed PCa, clinical-stage <T2b, Gleason score (GS) ≤3+4, PSA ≤15 ng/ml, and prostate volume (PV) ≤90 cc. Follow-up included transrectal ultrasound-guided prostate biopsy (TRUS) and PSA were evaluated at baseline and at 12-months, and additional follow-up (F/U) took place annually to 5 years. We evaluated MR-t by the cumulative maximum temperature (Tmax, 55 °C threshold) and thermal dose (cumulative equivalent minutes at 43 °C, 240 CEM43 threshold) delivered to the overall target volume and sub-volumes segmented into the transitional zone (TZ) and peripheral zone (PZ). Clinical outcome was represented by the PSA at 4-year follow-up.

Results: The nine men treated at our institution (mean±SD age of 67±5 years) had a total of 17 discrete lesions (9 GS 3+4; 8 GS 3+3). The mean F/U time was 40±13 months. No PCa was detected at 12-month F/U biopsy in 8/9 patients, and 2 PCa lesions (GG2) were detected in one patient. Mean±SD PSA decreased from 7.0±2.6 ng/ml on treatment day to 0.77±0.6 ng/ml (89%) at 1 month, stable to 4-years (p<0.001). The target region had median (IQR) volume of 37 (30-49) cc, median (IQR) Tmax 66°C (64-66°C), and thermal dose 9.5×105 CEM43 (5.8×105-2.8×106). In regions of adequate treatment the median (IQR) 81% (79-84)% of the target volume reached Tmax ≥55°C, and 95 (94-96)% received thermal dose ≥240 CEM43. In the TZ and PZ, median (IQR) Tmax was 72°C (70-73) and 64°C (62-66), respectively; thermal dose was 9.2×107 (1.3×107-3.5×108) CEM43 and 8.9×105 (1.8×105-1.1×106) CEM43 in TZ and PZ. In inadequately heated regions, 7.8% (6.1-11) and 16% (13-24) of the TZ & PZ had Tmax <55°C; 1.5% (1.4-1.7) of TZ and 3.8% (1.6-4.7) of TZ and PZ volumes had thermal dose <240 CEM43. Within 2.5 mm of the urethra, median (IQR) Tmax was 72 (70-74)°C, only 1.5 (0.2-2.0)% of the volume had Tmax≥86°C.

Conclusions: MRI-guided TULSA resulted in significant PSA reductions, as well as adequate treatment coverage in the prostate target volume in MR-t analysis of patients with low to intermediate grade PCa. Ultimately the relationship of treatment day energy deposition per region and clinical outcomes can help to inform the optimization of treatment parameters.

Figure 1. Changes in PSA during four years follow-up
MRI-Guided Focused Ultrasound Focal Therapy for Patients with Intermediate-Risk Prostate Cancer: A Phase 2b, Multicentre Study

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Background: Men with grade group 2 or 3 prostate cancer are often considered ineligible for active surveillance; some patients with grade group 2 prostate cancer who are managed with active surveillance will have early disease progression requiring radical therapy. This study aimed to investigate whether MRI-guided focused ultrasound focal therapy can safely reduce treatment burden for patients with localised grade group 2 or 3 intermediate-risk prostate cancer.

Materials and Methods: In this single-arm, multicentre, phase 2b study conducted at eight health-care centres in the USA, we recruited men aged 50 years and older with unilateral, MRI-visible, primary, intermediate-risk, previously untreated prostate adenocarcinoma (prostate-specific antigen ≥20 ng/mL, grade group 2 or 3; tumour classification T2) confirmed on combined biopsy (combining MRI-targeted and systematic biopsies). MRI-guided focused ultrasound energy, sequentially titrated to temperatures sufficient for tissue ablation (about 60–70°C), was delivered to the index lesion and a planned margin of 5 mm or more of normal tissue, using real-time magnetic resonance thermometry for intraoperative monitoring. Coprimary outcomes were oncological outcomes (absence of grade group 2 and higher cancer in the treated area at 6-month and 24-month combined biopsy) and safety (adverse events up to 24 months). This study is registered with ClinicalTrials.gov, NCT01657942, and is no longer recruiting.

Results: Between May 4, 2017, and Dec 21, 2018, we assessed 194 patients for eligibility and treated 101 patients with MRI-guided focused ultrasound. Median age was 63 years (IQR 58–67) and median concentration of prostate-specific antigen was 5·7 ng/mL (IQR 4·2–7·5). Most cancers were grade group 2 (78 [78%] of 101). At 24 months, 78 (88%; 95% CI 79–94) of 89 men had no evidence of grade group 2 or higher prostate cancer in the treated area. No grade 4 or grade 5 treatment-related adverse events were reported, and only one grade 3 adverse event (urinary tract infection) was reported. There were no treatment-related deaths.

Conclusions: 24-month biopsy outcomes show that MRI-guided focused ultrasound focal therapy is safe and effectively treats grade group 2 or 3 prostate cancer. These results support focal therapy for select patients and its use in comparative trials to determine if a tissue-preserving approach is effective in delaying or eliminating the need for radical whole-gland treatment in the long term.

Acknowledgment/Funding Sources: Funding Insightec and the National Cancer Institute.
Magnetic Resonance-Guided High Intensity Focused Ultrasound (MRgHIFU) to Treat Canine Appendicular Osteosarcoma: Preliminary Results

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Background: Osteosarcoma (OSA) is the most common bone tumor in dogs and children, making dogs an interesting naturally occurring bone tumor model for osteosarcoma research. In dogs, standard of care therapy includes amputation or limb sparing tumor resection followed by chemotherapy. When amputation is not an option, palliation of pain is usually provided through medical pain management and in some cases through palliative intent radiation therapy. Even when aggressive standard of care treatment is sought, median survival times of 235-540 days have been reported with the vast majority of patients developing lung metastasis within the first year.

Materials and Methods: The objectives of this ongoing pilot study are to: 1. Determine if MRgHIFU can successfully ablate canine appendicular osteosarcoma lesions, 2. Determine if MRgHIFU results in palliation of pain in dogs that do not undergo subsequent amputation, 3. Describe any complications related to MRgHIFU of appendicular OSA lesions. Dogs with confirmed appendicular OSA where owners decline standard of care amputation and chemotherapy are eligible for this study. Dogs with metastasis or prior treatment by radiation are not eligible.

Results: A 9-year-old Labradoodle with a distal radius osteosarcoma that was not a suitable candidate for amputation was treated with MRgHIFU as a palliative measure for osteosarcoma. Prior to HIFU treatment, the dog developed a grade 4/6 lameness that became unresponsive to medical management. 3D T1 and T2 weighted MRI scans were acquired on a Philips Achieva 3T scanner for treatment planning and 14 HIFU sonications ranging from 30-50W for 20s each were performed using the Profound Sonalleve V1 system. Near real-time thermometry confirmed adequate ablation temperatures (above 55°C but not above 80°C) within the bone lesion without concern for overheating the skin in the near field. No skin burns were detected via visual inspection. Histopathology confirmed coagulation necrosis within the targeted region. A grade 5-6/6 lameness was present at 24 hours following treatment that completely resolved over the following 96 hours. Radiographic evidence of tumor regression was evident 15 days post treatment. The dog remained lameness free for over 100 days. A second HIFU treatment was performed (41 sonications) at 105 days and led to a 1.5cm full thickness skin burn that healed by second intention. The dog remained lameness free for an additional 72 days but developed an unrelated infection in a hind limb 177 days following the first HIFU treatment and was euthanised. Post mortem examination confirmed a chondroblastic OSA of the right distal radius with marked regionally extensive fibrosis, osteolysis and reactive bone that were assumed to be the result of the HIFU treatment. There were also clusters of viable neoplastic cells visible in the distal radius. No gross or microscopic metastases were identified at post mortem examination. Severe necrotizing fasciitis (Streptococcus canis) and cellulitis of the right hind limb was confirmed with no identifiable cause. One additional patient has been treated thus far.
Conclusions: Preliminary results suggest that MRgHIFU can ablate canine appendicular OSA lesions and can provide sustained palliation of pain in dogs. It is likely that tumor size and location will affect the ability to treat and that the presence of mineralized tumor tissue could affect the risk for burn complications. Enrollment of additional cases is underway.

Acknowledgment/Funding Sources: Ontario Veterinary College Pet Trust Fund and Canada Foundation for Innovation
Investigating the Ablative and Immunological Outcomes of Histotripsy Treatment for Canine Osteosarcoma

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Background: Osteosarcoma (OS) is the most common bone malignancy in both canine and pediatric cancer patients with a greater incidence in canines than humans. Canine OS shares numerous biological, and genetic similarities with human OS, which allows the dog to serve as an informative comparative oncology research model for human OS. The risks associated with surgical resection of the primary tumor speak to the need for a non-surgical limb salvage treatment. Survival outcomes of a 5-year median survival for 70% of pediatric patients, and 10–12-month median survival for canine patients, have remained constant for the past several decades, with the leading cause of mortality being metastatic disease. Therefore, treatment options which have the potential to target not only the primary tumor, but also metastatic disease are profoundly needed. Histotripsy has the potential to serve as a non-invasive limb salvage option to treat the primary tumor and has immunomodulatory capabilities which may help mitigate metastatic disease progression.

Materials and Methods: The objective of our study was to investigate the ablative and immunological outcomes associated with histotripsy ablation of primary bone tumors in canine OS. A total of 10 dogs with suspected OS were enrolled into our study. A 2-3 cm spherical portion of the tumor was treated with histotripsy at a pulse repetition frequency of 500 Hz at a dose of 1,000 pulses/point. At 24 hours post histotripsy treatment all dogs underwent standard of care limb amputation surgery. Treated and untreated tumor samples were harvested and ablative outcomes were assessed grossly and microscopically via histopathological evaluation. Changes in the tumor immune microenvironment were assessed at both the cellular and molecular levels by comparing treated and untreated tumor samples. Peripheral blood samples were collected prior to treatment, at the time of surgery, and 2 weeks post treatment and circulating immune cell populations were evaluated via flow cytometry.

Results: Treatment was well tolerated by all patients, and precise targeted ablation was achieved and evident both grossly and microscopically. Ablated tumor tissue was characterized by hemorrhage, necrosis, and loss of viable tumor cells and cellular architecture and was clearly demarcated from the unablated tumor tissue. Within the tumor microenvironment we observed an upregulation in genes associated with immune response, regulation of inflammation, and natural killer cell mediated cytotoxicity in treated tumor samples compared to untreated samples. Our preliminary results indicate an observable increase in the proportion of circulating monocytes expressing CD80 and a decrease in peripheral monocyte TGF-b secretion post histotripsy treatment.

Conclusions: Current studies are ongoing to continue immune response evaluation at later time points post treatment. In conclusion our preliminary results suggest that histotripsy has both ablative and immunomodulatory potential and support the continued investigation of histotripsy ablation for primary bone tumors in canine OS patients.

Acknowledgment/Funding Sources: The Focused Ultrasound Foundation provided funding support for this project (Project ID FUSF-RAP-823R1).
Mechanical Effects of Low-Intensity FUS Pulsing on Murine Achilles Tendons

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Background: Tendons are dense connective tissues that efficiently transmit mechanical loads between muscle and bone, and therefore are critical to mobility. Tendinopathies (chronic tendon injuries) are characterized by decreased tendon mechanical properties, pain, swelling and loss of function, and if left untreated, may result in tendon rupture. Numerous treatment strategies exist to treat tendinopathies, but most show poor long-term outcomes. Mechanical loading (exercise-based rehabilitation) strategies are among the most efficacious treatments currently, and are the primary method of treatment across various tendinopathies. Evidence for the efficacy of therapeutic ultrasound (TUS) in stimulating tendon healing is limited due to inconsistencies in the ultrasound exposure conditions and inadequate stimulation likely due to its thermal nature. There remains a need to standardize such parameters and explore the potential of Focused Ultrasound methods (utilizing higher acoustic pressures delivered to a precise treatment volume, resulting in thermal and non-thermal bioeffects) in chronic models of tendon injury. The objective of the current study is to identify a narrow parameter space that emphasizes radiation forces in murine tendons resulting in tissue strains mimicking rehabilitative mechanical loading regimes, and evaluate the effects of such treatments on the mechanical properties and structural integrity of ex vivo murine Achilles tendons.

Materials and Methods: A custom 1.1MHz FUS transducer (H-102, Sonic Concepts, WA, USA) will be mounted onto a custom stereotactic positioning system to achieve precise targeting (Figure 1). The tendon body will be exposed to FUS treatments using parameters estimated from pilot experiments (Table 1). Hind limbs from 12-week old C57B1/6 male mice will be isolated, stored in saline and tested within 6 hours of isolation. Sample size calculation for the group comparisons will be based on an effect size of 0.7 (expected difference in tendon load-to-failure properties, which is our primary outcome measure) and 80% statistical power per an ANOVA design. Following these calculations, limbs will be randomly assigned to treatment groups. Ultrasound gel will be applied on the hind limb and the transducer will be positioned to cover the entire Achilles tendon body. Following FUS application, Achilles tendons will be designated for either tensile testing (stiffness, strength outcomes) or histologic assessment of collagen fiber

Table 1: FUS Pulsing Treatments

<table>
<thead>
<tr>
<th>Group</th>
<th>Type of Stimulation</th>
<th>Pressure (peak-peak) (MPa)</th>
<th>Duty Cycle (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild thermal (within therapeutic ranges)</td>
<td>0.5</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>Moderate thermal (within therapeutic ranges)</td>
<td>1.0-1.5</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>Very high thermal (non-therapeutic)</td>
<td>2.5-3</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>Moderate mechanical</td>
<td>5-10</td>
<td>1-5%</td>
</tr>
<tr>
<td>5</td>
<td>High Mechanical</td>
<td>10-20</td>
<td>1-5%</td>
</tr>
</tbody>
</table>

Figure 1. Experimental Set Up.
Experimental results will be validated using FEM simulations using COMSOL Multiphysics 5.4. A high-frequency ultrasound system (Sagacity Beamformer, Daxsonics Ultrasound, Inc) will be used to measure and quantify strains induced in the tendon due to FUS treatments.

**Results:** We expect that the COMSOL modeling will provide a detailed analysis of the types (e.g., tensile, shear) and magnitudes of strains to be expected from multiple pulsing regimes in consideration for our application. We expect that elastic modulus and maximum stress will be similar between untreated controls and mechanical-dominant treatment groups. We expect no histological evidence of tissue damage in any treatment groups.

**Conclusions:** We have previously demonstrated that it is possible to achieve a wide range of controlled thermal effects in murine Achilles tendons using low-intensity FUS application. Developing FUS regimens to elicit thermal and mechanical bioeffects ex vivo will facilitate future in vivo investigation of the efficacy of FUS treatments in the treatment of chronic tendon injuries.
Ultrasound-Guided Histotripsy Ablation in Feline Patients with Injection Site Sarcomas

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Background: Feline soft tissue sarcoma (STS) and injection site sarcoma (fISS) are rapidly growing tumors with low metastatic potential, but locally aggressive behavior. Aggressive surgery is used to remove the tumor, and many tumors cannot be completely resected due to delayed identification, diagnosis, and/or the location of the mass. As a result, there is a critical need for novel, non-invasive, and more effective therapies. Histotripsy is a non-thermal, non-invasive focused ultrasound therapy using controlled acoustic cavitation to mechanically disintegrate tissue. Histotripsy has been explored for the ablation of soft tissue sarcomas in dogs but has not been validated in feline patients with sarcomas. Additionally, preclinical in vitro and in vivo studies have shown that histotripsy ablation might induce immunogenic changes in the local tumor microenvironment and systemically. This study investigates the in vivo safety and feasibility of targeting and ablating superficial STS and fISS tumors with histotripsy in pet cats with spontaneous tumors, as well as, the immunogenic impact following a single histotripsy ablation.

Materials and Methods: In collaboration with the Virginia-Maryland Regional College of Veterinary Medicine, histotripsy ablation of STS and fISS was investigated in client-owned cats with spontaneous tumors. Patient-specific treatment plans were developed using pre-treatment CT (Fig. 1B) and ultrasound imaging. A custom 1 MHz histotripsy system was used to target tumors non-invasively and coupled to the patient using a container of degassed water (Fig. 1A,C). Ellipsoidal volumes within a portion of the tumor were treated with single cycle pulses applied at a pulse repetition frequency of 500 Hz and a treatment dosage of ~500 pulses per point. All treatments were monitored in real time using ultrasound imaging (Fig. 1D), and patient tumors were surgically resected 4 to 6 days after histotripsy treatment. To assess tumor ablation, gross morphological and histological analyses of the treated tissues were completed and compared against pre-treatment tumor biopsy samples by a board-certified pathologist. Routine hematoxylin and eosin (H&E) histopathology was used to assess treatment damage in the treated regions. Immunological analyses to characterize tumor-associated macrophages (TAMs) and tumor-infiltrating lymphocytes (TILs) are planned. Formalin-fixed, paraffin-embedded samples from treated tissue regions will be used to compare TAMs with IBA-1 and TILs with CD3 (pan-T-cell) and CD79a (B-cell) against pre-treatment samples and untreated sections of post-treatment samples. Ultrasound imaging was used to confirm the formation of the histotripsy bubble cloud during treatment.

Figure 1. A) Histotripsy system, transducer (insert), and treatment set-up. B) Pre-treatment CT image with tumor circled. C) Coupling bath positioned over the tumor. D) Treatment US image with visible bubble cloud. E) Patient tumor 1 day post-histotripsy treatment.
Results: Three cats with suspected injection site sarcomas were treated. In all three feline patients, no significant anesthetic events were reported, and histotripsy treatments were well-tolerated. Precise cavitation bubble clouds were generated in all patients and visible on real-time ultrasound imaging throughout the length of treatment (Fig. 1D). Complete histological and immunohistochemical analyses are pending; preliminary analysis of H&E stained tissues shows incomplete ablation of treated STS. In all patients, treated tissues exhibited mostly coagulative necrosis with regions of lytic necrosis and hemorrhage. The totality of ablation-induced necrosis varied between patients. In two of three patients, pre-focal cavitation at or near the skin’s surface was observed during treatment on ultrasound imaging and correlated with microscopic abnormalities identified histologically in the skin, including necrosis, edema, and hemorrhage. Gross areas of ulceration were also noted (Fig. 1E).

Conclusions: Results demonstrate the safety and feasibility of histotripsy to target and ablate superficial feline STS tumors. Pre-focal cavitation at the skin’s surface caused off-target damage to the skin and may have resulted in shielding of the therapy pulses, reducing treatment efficiency at the focus. Future studies will investigate optimized treatment doses and transducer designs for this application.

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Histotripsy Ablation of Spontaneously Occurring Canine Bone Tumors In Vivo

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Background: Osteosarcoma (OS) is a malignant, highly metastatic bone tumor that affects both dogs and humans. OS is treated through invasive limb amputation or limb salvage surgeries and chemotherapy. Even with these interventions, OS prognosis is poor and has been stagnant for decades, and novel, ideally non-invasive therapies are critically needed. Histotripsy is a non-thermal, non-invasive focused ultrasound (US) therapy using controlled acoustic cavitation to mechanically disintegrate tissue. Histotripsy has been explored preclinically and clinically for the ablation of soft tissue tumors, and ex vivo studies suggest that histotripsy may also be able to treat osteosarcoma tumors. In this study, the in vivo safety and feasibility of ablating bone tumors with histotripsy was investigated in canine patients with spontaneous, appendicular primary bone tumors.

Materials and Methods: Studies in collaboration with the Virginia-Maryland College of Veterinary Medicine investigated histotripsy ablation primary bone tumors in client-owned dogs. Patient-specific treatment plans were developed for histotripsy experiments using pre-treatment CT and US imaging. A 500 kHz histotripsy system was used to target tumors non-invasively and guided by real-time US imaging. Planned spherical ablation volumes of 1.25 to 3 cm in diameter were treated within a portion of the bone tumors using single cycle histotripsy pulses applied at a pulse repetition frequency of 500 Hz and a treatment dosage of 500 pulses per point. To compare the planned ablation volume against the achieved ablation volume, post-treatment contrast-enhanced CT images were collected for each patient. One day following histotripsy treatment, the dogs underwent standard-of-care amputation surgery of the affected limb. The ability of histotripsy to generate complete ablation of the targeted regions within the bone tumors was evaluated grossly and histologically by comparing treated and untreated regions of patient-matched tumor samples.

Results: Five canine patients with appendicular primary bone tumors (n = 4 osteosarcoma, n = 1 chondrosarcoma) were enrolled in the current study. Five bone tumor treatments were completed with treated volumes ranging from 1.022 to 14.14 cm3. Treated tumors varied in composition. Based on pre-treatment radiographic and CT imaging, two dogs had primarily proliferative bony lesions, two dogs had primarily lytic bony lesions, and one dog exhibited a more even mix of lytic and proliferative bony lesion. Three dogs also had a substantial soft tissue component to their bone tumor. The histotripsy treatment was well-tolerated in all patients, with no significant adverse events reported. Histotripsy bubble cloud formation was confirmed by US imaging and/or passive cavitation detection (PCD) in all patients at peak negative pressures averaging 29.59 ± 8.17 MPa. Visible bubble clouds on US imaging were formed in three of the five treatments. In the patients without cloud visibility on US, the presence of cavitation was confirmed by PCD signals at the focus similar to the PCD signals measured in the patients with visible bubble clouds. Gross

Figure 1. A) Photograph of patient tumor before treatment. B, E) Pre- (B) and post-treatment (E) CT images of tumor. C, F) Untreated (C) and treated (F) H&E stained tumor samples. D) US image of tumor with histotripsy bubble cloud visible during treatment (arrow).
analysis of treated samples revealed obvious foci of necrosis. Histologically, treated areas exhibited varying amounts of acute hemorrhage, lytic and coagulative necrosis, and matrix degeneration. Occasionally, foci of viable cells remained within targeted treatment regions. Post-treatment CT scans demonstrated no significant differences compared to pre-treatment scans. Post-treatment CT scans did show a mild increase in soft tissue swelling and areas of diminished enhancement in the soft tissue component of the tumors, but no identifiable characteristics of ablation damage.

Conclusions: Results from this initial in vivo feasibility study demonstrate that histotripsy has the potential to be used for the non-invasive ablation of bone tumors. Significant challenges remain and must be addressed in future work to accurately track and monitor cavitation bubble clouds during bone tumor treatments. Ongoing studies are investigating histotripsy ablation of entire canine bone tumors and improved techniques for assessing post-treatment ablation zone volumes using MRI.

Acknowledgment/Funding Sources: This work was funded by the American Kennel Club Canine Health Foundation (Canine Health Foundation No. 02773) and the National Institutes of Health (Project ID 1R21EB030182-01).
Mechanical High-Intensity Focused Ultrasound (Histotripsy) in Dogs with Spontaneously Occurring Soft Tissue Sarcomas

Ester Yang1, Lauren N. Ruger2, Jessica M. Gannon3, Hannah Sheppard2, Sheryl Coutermash-Ott2, Timothy Ziemlewicz4, Nikolaos Dervisis5, Irving C. Allen2, Gregory B. Daniel5, Eli Vlaisavljevich2, Shawna Klahn5

1Animal Cancer Care and Research Center, Virginia-Maryland College of Veterinary Medicine, Ashburn, VA, USA
2Virginia Polytechnic Institute and State University, Blacksburg, VA, USA
3Virginia Tech - Wake Forest School of Biomedical Engineering and Sciences, Blacksburg, VA, USA
4University of Wisconsin, Madison, WI, USA
5Virginia-Maryland College of Veterinary Medicine, Roanoke, VA, USA

Background: Histotripsy is a non-thermal, non-invasive high-intensity focused ultrasound (HIFU) ablative technique that causes mechanical fragmentation of tissue, resulting in liquefied acellular debris with histologically clear demarcated boundaries between treated and non-treated tissues. The acellular debris may include tumor antigens with preserved immunogenicity and the potential to generate systemic immune response against tumor cells. Soft tissue sarcomas (STS) are a common form of cancer in dogs with biological behavior similar to STS in humans. Long-term tumor control requires complete removal with extensive surgical resection, which in many cases is not feasible. As a result, there is need for alternative therapies. The primary objective of this study was to demonstrate safety and feasibility of histotripsy in a large animal model of spontaneous STS. The secondary objective was to characterize the impact of histotripsy on the immunologic response.

Materials and Methods: Pet dogs diagnosed with spontaneous STS were recruited. CT scan of the chest, abdomen, and the tumor was performed for staging and treatment planning. Pretreatment biopsies were obtained. Safety was monitored with physical examinations, owner reports, and CBC/serum biochemistry. Partial tumor ablation was performed using a 500 kHz prototype histotripsy system. A spherical treatment zone of up to 3 cm diameter in each tumor was treated with histotripsy according to the patient-specific treatment plan using 1-2 cycle pulses applied at a pulse repetition frequency (PRF) of 500 Hz. Anatomical ablation zones were evaluated with contrast CT at 1- and 4-days post-treatment, with tumor resection at 4-6 days post-treatment. Tumor microenvironment (TME) gene expression was evaluated with the Nanostring Canine IO panel, and the systemic immune response was evaluated using multiplex serum cytokine levels.

Results: Ten dogs were recruited and treated. Tumor histologies included 3 grade III STS, 4 grade II STS, 2 grade I STS, and 1 malignant mesenchymoma. Six dogs are alive, three dogs were euthanized due to disease progression, and one dog was lost to follow up. Histotripsy-related complications were generally self-limiting, with only one patient having increased cutaneous injury score from 1 to 2 (scale 1-5) post-treatment, likely due to prefocal cavitation at the skin. No significant adverse events impacting patient outcome were noted in any of the patients. Visible histotripsy cavitation bubble clouds were seen on real-time ultrasound imaging in nine of ten treatments. Post-treatment histopathology indicated sharply-defined regions of ablation that were clearly identifiable grossly and histologically in all samples. Treatment zones were characterized by loss of cell viability, hyalinization, and acute hemorrhage. Posttreatment contrast-enhanced CT images revealed clear, demarcated regions of histotripsy ablated tissue in seven of ten patients. Differential gene expression analysis identified 79 genes with at least 2-fold change following treatment. Genes associated with inflammation, immune cell migration, and immune cell interactions were the highest upregulated. Amongst the gene set analyses, the myeloid compartment gene sets obtained the highest significance score. There were no statistically significant differences between pre- and post-treatment cytokine concentrations for any of the analytes.

Conclusions: Histotripsy can achieve safe and effective tumor ablation in dogs diagnosed with STS. Histotripsy induced pro-inflammatory changes within the tumor microenvironment. Histotripsy as an immunotherapeutic treatment option needs to be further investigated. Histotripsy has a potential to be a precise, non-invasive treatment for canine STS.

Acknowledgment/Funding Sources: This research was funded by the Focused Ultrasound Foundation (Grant #453047). Shawna Klahn was supported by iTHRIV Scholars Program
(supported in part by the NIH National Center for Advancing Translational Sciences, UL1TR003015 and KL2TR003016).
Ferenc Jolesz Memorial Award

Graeme Woodworth, MD

The Ferenc Jolesz Memorial Award was established in 2016 to honor the life of a true pioneer in focused ultrasound. The award has a two-fold purpose: to honor Ferenc’s memory and to recognize and encourage this same innovative spirit in mid-career researchers and clinicians who continue to advance focused ultrasound.

We are honored to present the award to Graeme Woodworth, MD.

Dr. Woodworth is Professor and Chair of Neurosurgery at the University of Maryland School of Medicine and Director of its Brain Tumor Treatment & Research Center.

Dr. Woodworth’s research focuses on improving treatments for malignant brain tumors, including the deadliest adult primary brain tumor, glioblastoma (GBM). He is investigating the use of focused ultrasound to open the blood-brain barrier (FUS-BBBO) to enhance drug delivery to brain-invading tumor cells – the major source of GBM recurrence. His team completed the first clinical trial of FUS-BBBO in the United States and is developing and conducting new pivotal studies to support device approval by the FDA. Ultimately, he aims to leverage this work to improve survival for patients with GBMs and establish focused ultrasound as a new therapeutic modality for GBM and other devastating brain diseases.

"It is a true honor to receive the Jolesz Award. While I did not have the opportunity to meet Dr. Jolesz, his work and his life in neurosurgery and image-guided therapy are inspirations for me. Dr. Jolesz was a fearless pioneer and helped launch noninvasive, image-guided focused ultrasound therapy for numerous neurological disorders. I hope to embody Dr. Jolesz’s spirit in advancing new devices and clinical applications of focused ultrasound."

The Ferenc Jolesz Memorial Award is supported by INSIGHTEC. Dr. Woodsworth formally accepted the award, which includes a $5,000 cash prize, and presented his research at the 8th International Symposium on Focused Ultrasound during the awards ceremony on Monday, October 24, 2022.

In Memoriam — Ferenc Jolesz, MD

Ferenc Jolesz, MD, was a world-class visionary whose passion for pushing surgery into the 21st century led from developing image-guided minimally invasive therapy to pioneering focused ultrasound as a completely noninvasive approach. He passed away suddenly in December 2014.

Dr. Jolesz helped create the world’s first MR-guided focused ultrasound system, and an early device was installed at Brigham and Women’s Hospital. Research was conducted for several years under his guidance, eventually leading to the FDA approval of a system to treat uterine fibroids and establishing the technology’s potential to noninvasively treat a range of serious medical conditions. Dr. Jolesz spent the last few years of his life championing the use of focused ultrasound for the brain, and was especially interested in exploring treatments for Alzheimer’s disease.
2022 Clinical Adoption Award

Professor Zhibiao Wang, MD

The newly established Clinical Adoption Award recognizes an individual dedicated to advancing the field of focused ultrasound and whose efforts have led to a significant number of patient treatments.

We are honored to recognize Professor Zhibiao Wang, MD with the inaugural Clinical Adoption Award.

In 1999, Prof. Wang founded Chongqing Medical Focused Ultrasound Technology Development Co., Ltd. (later renamed Chongqing Haifu Medical Technology Co. Ltd.) and now serves as the chairman. He leads the company’s research in the fields of device development, clinical application, and marketing.

Prof. Wang developed the company’s – and China’s – first high-intensity focused ultrasound therapeutic system that is used to treat malignant tumors (e.g., liver cancer, pancreatic cancer, breast cancer, osteosarcoma, soft tissues sarcoma) and a wide range of benign diseases — such as uterine fibroids and adenomyosis. The Chongqing Haifu device has been exported to 28 countries and regions and has collectively treated more than 200,000 patients with benign and malignant tumors worldwide.

The company has since developed a series of focused ultrasound therapeutic devices to treat non-tumor diseases, such as disease of the vulva surface and cervix, osteoarthritis, allergic rhinitis, soft tissue injury, pain, and more.

Prof. Wang's career in therapeutic ultrasound has spanned 34 years. He has made pioneering contributions to the field of ultrasound therapy, including breakthroughs in basic research, large medical equipment development, clinical applications, and industry standards.

He is a Professor of Medicine and leads the State Key Laboratory of Ultrasound in Medicine and Engineering at Chongqing Medical University in China.

His contributions to therapeutic ultrasound research have garnered major funding grants and second prize in both the National Technology Invention Award and the National Science and Technology Progress Award. He has published more than 50 scientific papers in leading journals of the field of ultrasound medicine.

“Prof. Wang is a pioneer in the development of focused ultrasound as a revolutionary, noninvasive therapy and its commercialization,” said Foundation Chairman, Neal F. Kassell, MD. “The company he founded is a leading manufacturer of focused ultrasound equipment, and he has had an immeasurable impact on the technology's trajectory from idea to its adoption as a global standard of care for a wide variety of serious medical disorders.”

Prof. Wang earned his MD from Chongqing Medical University and has been practicing as an Ob-Gyn specialist.

During the awards ceremony on Sunday, October 23, 2023, Prof. Wang formally accepted the award.
2022 Lifetime Achievement Award

Yoav Medan, PhD

The Lifetime Achievement Award was established in 2022 and recognizes an individual who has devoted a major portion of his or her distinguished career to advancing focused ultrasound therapy by establishing the field and improving the lives of patients.

We are honored to recognize Yoav Medan, PhD, with the inaugural Lifetime Achievement Award.

Dr. Medan is among the elite pioneers of focused ultrasound therapy and has dedicated more than 23 years to advancing the field.

He received his PhD from the Technion, Israel Institute of Technology in 1984 and a business administration diploma from the University of Bradford in 1995.

In 1999, he joined device manufacturer Insightec and served as Vice President & Chief Systems Architect for more than a decade. During his tenure at Insightec, Dr. Medan designed and implemented a robotic system, defined the software of the treatment systems to expand its capabilities for innovative early research, managed the engineering effort of the brain preclinical system, and implemented a fast method for assuring the safe and correct output of installed focused ultrasound treatment devices.

In addition, he supported luminary research sites in demonstrating future applications on the Insightec platform, such as treating a moving liver with real-time target tracking and thermometry and demonstrating neural modulation in mice.

He is currently a member of the Foundation’s Scientific Advisory Board and has been influential in developing the technology behind FUSMobile, a focused ultrasound company addressing low back pain.

In 2011, Medan’s inspirational TEDMED presentation introduced focused ultrasound to countless individuals and inspired researchers to explore the technology. The video has been viewed more than 870,000 times.

“On behalf of the entire Foundation team, I am pleased to recognize Yoav for his dedication to the field of focused ultrasound,” said Foundation Chairman Neal F. Kassell, MD. “He has made a significant impact in the effort to establish this innovative and disruptive technology as the highly regarded field of medicine it is today.”

Dr Medan formally accepted the award during the awards ceremony on Sunday, October 23, 2023.
2022 Visionary Award

Professor Gail ter Haar, DSc

Established in 2014, the Visionary Award is given every two years at our Symposium to recognize an individual who has created a larger vision for what the future of focused ultrasound may hold and whose effort, passion, and persistence have been crucial to advancing the field.

We are honored to present the award to Professor Gail ter Haar, DSc.

Prof. ter Haar leads the therapeutic ultrasound team at The Institute for Cancer Research (ICR), where her work centers on understanding how ultrasound interacts with tissue. Her most recent research has involved developing devices and protocols for ultrasound-based treatments of cancer, investigating focused ultrasound for immune stimulation, and using focused ultrasound to treat liver and kidney tumors.

In 2014, her team at ICR – along with colleagues at the Royal Marsden Hospital – were recognized as a Focused Ultrasound Center of Excellence. The group has completed focused ultrasound clinical trials for gynecological tumors and bone pain. Currently, her team is involved in a Foundation-funded trial aiming to use focused ultrasound to resolve twin-twin transfusion syndrome.

Prof. ter Haar is the founding President of the International Society for Therapeutic Ultrasound (ISTU). She is also an honorary member of the British Medical Ultrasound Society (BMUS) and the Society of Thermal Medicine (STM), honorary fellow of the American Institute for Ultrasound in Medicine (AIUM), and fellow of both the Acoustical Society of America (ASA) and the Institute of Physics and Engineering in Medicine (IPEM).

She leads the UK-based ThUNDDAR (Therapy Ultrasound Network for Drug Delivery and Ablation Research) network, which promotes collaboration between British and European groups working with therapeutic ultrasound. Prof. ter Haar is deputy editor of Ultrasound in Medicine and Biology, associate editor of Ultrasonics, and on the editorial boards of International Journal of Hyperthermia and Medical Physics. She has written five books, 32 book chapters, and more than 250 peer reviewed research papers.

“Gail’s contributions to the field of focused ultrasound are truly immeasurable,” said Foundation Chairman Neal F. Kassell, MD. “She has led pioneering basic science and translational research that has ultimately impacted many patient lives. Additionally, her dedication to fostering collaboration among researchers – and creating a means to do so by establishing ISTU – has helped galvanize the focused ultrasound community.”

During the awards ceremony on Sunday, October 23, 2023, Prof. ter Haar formally accepted the award.
The newly established Commercialization Pathfinder Award recognizes an individual who has served as a galvanizing force in facilitating the rapid acceleration of focused ultrasound, speeding the transition from laboratory research to widespread adoption and utilization of the technology. The recipient is always working to achieve the ultimate goal – providing significant contributions to the use of focused ultrasound technology to decrease death, disability, and suffering for patients with serious medical disorders around the world.

We are honored to present Kobi Vortman, PhD, with the inaugural Commercialization Pathfinder Award.

Dr. Vortman’s career in focused ultrasound began as president of Elbit Medical Imaging, where he was responsible for developing the company’s proprietary MR-guided focused ultrasound technology. It was this technology that launched Insightec in 1999 as part of a joint effort by Elbit and GE Healthcare.

Dr. Vortman served as INSIGHTEC’s Chief Executive Officer until 2016, when he transitioned to his current role. For the past 23 years, INSIGHTEC has been an industry leader in advancing focused ultrasound for many disorders, and this is in large part due to Dr. Vortman’s vision. The company’s Exablate system was the first focused ultrasound device to be approved by the US Food and Drug Administration when it earned the recognition in 2004 to treat uterine fibroids. Various versions of the system have since earned approvals globally to treat essential tremor, Parkinson’s disease, bone metastases, prostate cancer, arthritis, depression, neuropathic pain, obsessive-compulsive disorder, and more.

Eyal Zadicario, PhD, Insightec’s Chief Operating Officer and General Manager, joined INSIGHTEC when it was founded in 1999 and has worked alongside Dr. Vortman during his tenure.

“Kobi has focused his and the team’s efforts on transforming focused ultrasound from a vision into a reality,” says Dr. Zadicario. “His extraordinary journey – realizing the potential, founding Insightec, overcoming unprecedented scientific challenges, and guiding the company through clinical evidence approval and acceptance – has positioned the technology at the leading edge of neurosurgery. He is an example to us all for the passion, dedication and professionalism it takes to make breakthroughs happen.”

Dr. Vortman formally accepted the award during the awards ceremony on Sunday, October 23, 2023.
Young Investigator Awards Program

The Focused Ultrasound Foundation established the Young Investigator Awards Program to encourage quality research by clinicians and scientists-in-training and to support their presentation of meritorious scientific papers at venues such as the 7th International Symposium on Focused Ultrasound.

Graduate students, research fellows, clinical fellows, and junior faculty members are eligible to apply for this early-career honor, which includes a $1,000 cash award. One of the 2020 Young Investigator Awards is sponsored by Bracco Suisse SA.

Nine Young Investigators are participating in the 7th International Symposium on Focused Ultrasound and being acknowledged with a special logo to call attention to their presentations on the virtual symposium platform. They recorded oral presentations and had an opportunity to participate in the question-and-answer sessions for the topical area of their research. To emphasize the significance of the Young Investigator Awards, the Foundation announced this year’s award recipients in our monthly e-newsletter.
2022 Young Investigator Awards

Abdul-Kareem Ahmed, MD
Awarded for: Bilateral MR-Guided Focused Ultrasound Central Lateral Thalamotomy for Refractory Trigeminal Neuralgia: Preliminary Results [CP-01-YI]

Abdul is a 5th year neurosurgery resident at the University of Maryland. He is involved with clinical trials using MRgFUS to treat movement disorders, pain, and brain tumors. Abdul also has an interest in improving the treatment envelope of this technology, in order to reach more patients in need.

Javier Ajenjo Barcenas, PhD
Awarded for: PAM and FUS-assisted AAV Delivery into the Brain for Quantitative PET/CT Imaging [GT-01-YI]

Javier received his MSci from the University Complutense in Madrid (Spain). He then moved to Prague (Czech Republic) where he earned his PhD degree in Chemistry from Univerzita Karlova under the supervision of Dr Petr Beier at IOCB, working on the synthesis and derivatization of hypervalent sulfur fluorides. During this period, he also took part as ESR of FLUOR21 initial training network led by Prof Graham Sandford (Durham University) and collaborated with F2 Chemicals Ltd. Later, he joined the University of Oxford (UK) as a postdoctoral research fellow to work on the synthesis and biological evaluation of F18-labeled ATM inhibitors under the supervision of Prof Bart Cornelissen. In 2021, he joined Ferrara lab as a postdoctoral scholar to work on the development of radiochemistry methods and the synthesis of therapeutics for medical imaging.

Ali Bassir, MD
Awarded for: Pivotal Study of Transurethral Ultrasound Ablation of the Prostate: MR Thermometry Parameters and Clinical Response at 4-year Follow-up [URO-02-YI]

Ali Bassir is a research fellow in the radiology department at David Geffen School of Medicine at UCLA. His research is focused on abdominal imaging, especially on prostate, pancreas, and liver cancer. Detection and differentiation of lesions with advanced imaging modalities like multiparametric MRI and contrast-enhanced ultrasound are his main area of interest.
2022 Young Investigator Awards | continued

Sheng Chen
Awarded for: Simultaneous Monitoring of Bone and Soft Tissue with a Rapid MRI Method for Focused Ultrasound Surgery [BRT-08-YI]
University of Virginia, Charlottesville, VA, United States

Riccardo Ciocca
Awarded for: A Non-invasive Biomarker of Microbubbles Distribution in the Brain: Comparison between Intraoperative CEUS and Perfusion MRI [BRT-11-YI]
Fondazione IRCCS Istituto Neurologico Carlo Besta, Treviglio, Bergamo, Italy

Daniel Düx, MD
Awarded for: A 10-year Multicenter Experience of MR-guided High Intensity Focused Ultrasound (MRgFUS) in 105 Patients with Extra-Abdominal Desmoid Tumors [MSK-02-YI]
University of Hannover (MHH), Hannover, Niedersachsen, Germany
**Areej Ennasr**

Awarded for: Examination of Low-Intensity Focused Ultrasound (LIFU) Parameters and Longevity of Effect for Human Neuromodulation [NMD-01-YI]

Virginia Tech Carilion School of Medicine, Fairfax, VA, United States

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**Yutong Guo, PhD**

Awarded for: Microbubble Properties and Ultrasound Frequency can Modulate the Blood-Brain Barrier Phenotype [BRT-18-YI]

Georgia Institute of Technology, Norcross, GA, United States

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**Alayna Hay, PhD**

Awarded for: Investigating the Ablative and Immunological Outcomes of Histotripsy Treatment for Canine Osteosarcoma [VET-02-YI]

Alayna Hay is a postdoctoral research associate in Dr. Joanne Tuohy's lab at the Virginia Tech Animal Cancer Care and Research Center, part of the Virginia Maryland College of Veterinary Medicine. Researchers there investigate the immune response associated with histotripsy ablation and osteosarcoma. The lab utilizes in-vitro models, preclinical murine models, and client-owned dogs with spontaneously occurring osteosarcoma to accomplish our research goals.
2022 Young Investigator Awards | continued

**Alexander In**
Awarded for: Low-Intensity Focused Ultrasound to Insula Attenuates Contact Heat Evoked Potentials and Reduces Pain Perception in Humans [CP-02-YI]
Virginia Tech Carilion School of Medicine, Roanoke, VA, United States

**Ayesha Jameel**
Awarded for: The Evolution of Thalamic Ventral Intermediate Nucleus Targeting in MRgFUS Thalamotomy for Tremor, an International Perspective 2019 to 2021 [MOV-16-YI]
Imperial College, London, United Kingdom

**Sara Johnson, PhD**
Awarded for: Non-Contrast MR Biomarker of Thermal Ablation in MRgFUS Treatments via Supervised Learning to MR-Registered Histology [TEC-05-YI]
University of Utah, Salt Lake City, UT, United States
Ryan Jones, PhD

Ryan M. Jones received the PhD in Medical Biophysics from the University of Toronto. Dr. Jones is currently a Senior Research Engineer-Physicist in the Focused Ultrasound (FUS) Laboratory at Sunnybrook Research Institute (SRI). He is a member of the clinical team performing MR-guided FUS patient treatments at SRI.

Stephen Lee
Awarded for: Focused Ultrasound Modulates Neuropathic Pain [CP-04-YI]

Columbia University, New York, NY, United States

Xiaoyue Li
Awarded for: Real-Time Harmonic Motion Imaging Guided Focused Ultrasound (HMigfUS) in Breast Cancer Patients in Vivo [BST-04-YI]

Columbia University, New York, NY, United States
2022 Young Investigator Awards | continued

**Katherine Liu**
Awarded for: Safety and efficacy of single-treatment neuronavigation-guided FUS to induce blood-brain barrier opening in Alzheimer's disease patients [NDG-07-YI]
Columbia University, New York, NY, United States

**Veronika Purrer, MD**
Awarded for: Quantitative and Qualitative Tremor Evaluation after tcMRgFUS Thalamotomy in ET [MOV-24-YI]
University Hospital Bonn, Bonn, Nordrhein-Westfalen, Germany

**Lauren Ruger**
Awarded for: Investigating the Ablative and Immunological Outcomes of Histotripsy Treatment for Canine Osteosarcoma [VET-02-YI]
Virginia Tech, Blacksburg, VA, United States
Tao Sun, PhD
Awarded for: Focused Ultrasound Immunomodulation on the Myeloid Compartment of the Brain in Treating GBM and Alzheimer’s Disease [IMM-15-YI]

Tao Sun is currently an Instructor of Radiology at Harvard Medical School, and a Research Associate in Bioengineering at Harvard University. He will join Northeastern University as an Assistant Professor of Bioengineering starting from January 2023. The goal of his research program is to unveil how focused ultrasound (FUS) modulates the neuroimmune interface and to develop techniques of ultrasound immunomodulation and cell-based theranostics for treating neurological disorders, such as glioblastoma and Alzheimer’s disease. Tao has received many recognitions for his scientific contributions to the fields of FUS, drug delivery, cancer immunoengineering, and neuroimaging. Some of his first-author works were published in high-profile journals including PNAS, Journal of Controlled Release, Applied Physics Letters, Advanced Drug Delivery Reviews, and were featured in mainstream science and technology media including WIRED (https://www.wired.com/story/the-second-coming-of-ultrasound/), Science Daily, and Medical Xpress.

Dezhuang (Summer) Ye, PhD
Awarded for: Ultrasound with Microbubbles Accelerates Glymphatic Transportation [BRT-44-YI]; Focused Ultrasound-Mediated Intranasal Delivery of AAV to Targeted Brain Regions with Minimal Systemic Exposure [GT-06-YI]

Dezhuang Ye is currently a postdoctoral researcher in Prof. Hong Chen’s Lab at Washington University in Saint Louis. She earned her PhD in 2021 from Washington University in Saint Louis. Her current interests include FUS-guided brain drug delivery and gene therapy, as well as FUS mediated glymphatic transportation.
The Focused Ultrasound Foundation’s Summer Internship Program was established in 2012 with the goal of giving accomplished high school, undergraduate, and graduate students the opportunity to collaborate with leaders in the field on a variety of projects that address preclinical, clinical, and business challenges.

In May 2018, the Foundation’s internship program—which encompasses both local and global interns—was named in memory of Board of Directors member Charles Steger, PhD. The Foundation’s summer technical internships are generously funded by the Claude Moore Charitable Foundation. The Claude Moore Summer Internship Program is part of the Charles Steger Focused Ultrasound Internship Program and is designed to foster interest in focused ultrasound technology among the next generation of researchers.

In the summers of 2021 and 2022, students and recent graduates worked on a range of projects, and the Foundation’s Director of Extramural Research, Matt Eames, PhD, coordinated a Zoom lecture series focusing on various facets of focused ultrasound.
Global Internship Program

The Focused Ultrasound Foundation offers an international internship opportunity for high school and university undergraduate students interested in the physical and life sciences. Interns supported through this program work in an established focused ultrasound laboratory under a researcher recognized in the field.

2021 Global Interns

**Sena Akgun**
St. Mary’s Hospital  
Mentor: Wladyslaw Gedroyc, MD

**Lucas Berens**
University of Cincinnati  
Mentor: Kenneth Bader, PhD

**Dan Budiansky**
Sunnybrook Health Sciences Centre  
Mentor: Nir Lipsman, MD, PhD

**Alexandra Butnariu**
Ohio State University  
Mentor: Vibhor Krishna, MD

**MacKenzie Campbell**
Hospital for Sick Children  
Mentor: Adam Waspe, PhD

**Davi Cavinatto**
Brigham Young University  
Mentor: Steven Allen, PhD

**Riccardo Ciocca**
Istituto Neurologico Carlo Besta  
Mentor: Francesco Prada, MD

**Nicoletta Corradino**
Istituto Neurologico Carlo Besta  
Mentor: Francesco Prada, MD

**Ioannis Demetriades**
Cyprus University of Technology  
Mentor: Christakis Damianou MS, PhD

**Elizabeth Douglas**
University of Toronto  
Mentor: Meaghan O’Reilly, PhD

**Lee Hyo Jin**
Jeju National University  
Mentor: Dong-guk Paeng, PhD

**Matthew Jordan**
Stanford University  
Mentor: Raag Airan, MD, PhD

**Azamat Kaloev**
Moscow State University  
Mentor: Oleg Sapozhnikov, PhD

**Gabriel Koh**
University of Washington  
Mentor: Pierre Mourad, PhD

**Erica Lin**
Vanderbilt University  
Mentor: Charles Caskey, PhD

**Joshua Marchant**
University of Utah  
Mentor: Dennis Parker, PhD

**Sabine Meurs**
University of Michigan  
Mentor: Mario Fabiilli, PhD

**Matt Osburn**
Brigham Young University  
Mentor: Steven Allen, PhD

**Alexander Robertson**
Columbia University  
Mentor: Elisa Konofagou, PhD

**Isabelle Stephen**
University of Maryland  
Mentor: Victor Frenkel, PhD

**Raya Subah**
University of Calgary  
Mentor: Samuel Pichardo, PhD

**Henry Tan**
University of Washington  
Mentor: Pierre Mourad, PhD

**Ryo Tsuda**
Brigham and Women’s Hospital  
Mentor: Nick Todd, PhD

**Kseniia Tumanova**
Moscow State University  
Mentor: Vera Khokhlova, PhD

Receiving the highest peer-reviewed rating among submissions from the 2021 and 2022 FUSF Global Interns, Elizabeth “Swanee” Douglas’ abstract, entitled “Investigation of Microbubble Response to Short Burst Phase Keying Ultrasound Exposures for Blood-Spinal Cord Barrier Opening” earned them an award and an opportunity to present their work at the symposium.
2022 Global Interns

Alexandra Brevde  
Brigham and Women’s Hospital  
Mentor: Nathan McDannold, PhD

Gianmarco Cei  
Scuola Superiore Sant’Anna  
Mentor: Arianna Menciassi, PhD

Eleni Christofi  
Cyprus University of Technology  
Mentor: Christakis Damianou, MS, PhD

Evan Conger  
Brigham Young University  
Mentor: Steven Allen, PhD

Kaizer Contreras  
University of Washington  
Mentor: Pierre Mourad, PhD

Renata Farrell  
Virginia Polytechnic Institute and State University  
Mentor: Eli Vlaisavljevich, PhD

Nartov Fedor  
Moscow State University  
Mentor: Vera Khokhlova, PhD

Chrisssa Fosocolos  
Columbia University  
Mentor: Elisa Konofagou, PhD

Gabriel Gallegos  
Loyola University  
Mentor: Muna Aryal, PhD

Michelle Hamani  
University of Toronto  
Mentor: Robert Chen, MA, MBChir

Wesley Judd  
University of Utah  
Mentor: Henrik Odeen, PhD

Zachary Olivier  
Brigham Young University  
Mentor: Steven Allen, PhD

Aarav Parikh  
University of Utah  
Mentor: an Kubanek, PhD

Veronica Percuoco  
Istituto Neurologico Carlo Besta  
Mentor: Francesco Prada, MD

Emily Smith  
University of Utah  
Mentor: Viola Rieke, PhD

Oleg Solontsov  
Moscow State University  
Mentor: Oleg Sapozhnikov, PhD

Na Sori  
Jeju National University  
Mentor: Dong-guk Paeng, PhD

Eddie Wang  
University of Michigan  
Mentor: Zhen Xu, PhD

Andrew Xie  
University of Calgary  
Mentor: Samuel Pichardo, PhD

Maya Yie  
Columbia University  
Mentor: Elisa Konofagou, PhD

Noah Zahn  
Loyola University  
Mentor: Muna Aryal, PhD
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INSIGHTEC® is a global healthcare company creating the next generation of patient care by realizing the therapeutic power of acoustic energy. The company’s Exablate technology focuses sound waves, safely guided by MRI, to provide treatment to patients with Prostate Disease, Essential Tremor and Parkinson’s Disease. Research for future applications is underway in partnership with leading academic and medical institutions.

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Silver Sponsors

NaviFUS Corporation
navifus.com
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NaviFUS is a tech-humanist —
We make innovative and human-centred technology that can transform CNS disease patients’ lives.

Our Vision
NaviFUS is a Biotech company dedicated to providing novel platform solutions for crossing the blood-brain barrier (BBB) for enhanced oncology drug delivery. Our product, the NaviFUS® System, is designed to utilize non-invasive ultrasound energy to enable transient and safe enhancement of BBB permeability to facilitate the transport of small or large molecular CNS drugs to target tumour tissue at high precision for better treatment outcomes and suppress seizures in epilepsy patients.

Our vision is to benefit CNS disease patients locally and globally by bringing the non-invasive BBB opening/neuromodulation focused ultrasound technology to clinical use through partnerships with global pharmaceutical companies, academic and hospital organizations, and federal agencies.

Our Solutions
NaviFUS® Neuronavigation-guided focused ultrasound system
The NaviFUS® system is a focused ultrasound technology platform that provides personalized and transformative solutions for brain diseases like glioblastoma and epilepsy. It can non-invasively open the BBB to allow large-molecular weight drug delivery to previously unreachable parts of the brain and suppress seizures in epilepsy patients.

NaviFUS — Saving Lives with Good Vibes
Verasonics designs and markets leading-edge Vantage™ Research Ultrasound Systems for academic and commercial investigators. These real-time, software-based, programmable ultrasound systems accelerate research by providing unsurpassed speed and control to simplify the data collection and analysis process.

Researchers across the globe use the Vantage platform to advance the art and science of ultrasound through their own research efforts. In addition, every Vantage System can be upgraded to any configuration - protecting capital equipment investments and expanding research options. Verasonics’ Vantage Systems are the ideal solution for ultrasound-driven research and development in biomedical, materials science, earth sciences, and the physics of acoustics.

Brainlab is a digital medical technology pioneer founded in 1989 and headquartered in Munich. The company employs more than 2000 people in 25 locations around the globe. Brainlab serves physicians, medical professionals and their patients in over 6000 hospitals in 121 countries.

Brainlab creates software-driven medical solutions that digitize, automate and optimize clinical workflows for neurosurgery, spine, trauma, craniomaxillofacial (CMF), general and vascular surgery as well as radiotherapy and radiosurgery. Core products center around surgical navigation, radiotherapy, digital operating room integration, and information and knowledge exchange. The Brainlab open framework operating system will allow third parties to develop medical applications to further advance the field of spatial computing and mixed reality.

Brainlab is dedicated to creating an impact in healthcare. The company connects opportunities from emerging digital technologies to transform healthcare at scale and help improve the lives of patients worldwide. For more information, please visit Brainlab and follow on LinkedIn, Twitter, Facebook and Instagram.

Sonablate Corp. is a world leader in minimally invasive focused ultrasound technologies. Sonablate Corp. designs and manufactures medical devices, including Sonablate® HIFU, the most customizable focal therapy treatment.

The Sonablate device has 510(k) clearance in the U.S, NMPA (National Medical Products Administration) approval in China; CE Marking in the EU and has obtained regulatory authorization in more than 50 countries outside the U.S.
At Theraclion, we believe that surgery as we know it is outdated. It generates excessive anxiety in patients and turns doctors into the executors of an archaic system. On the other hand, it subjects the health care system to tensions that are difficult to sustain. We therefore wanted to shake up this convention by creating an extracorporeal treatment device. Our solution replaces surgery with a robotic treatment that directs high-intensity focused ultrasound (HIFU) from outside the body. Our state-of-the-art ultrasound therapy device has already obtained CE mark for the non-invasive treatment of varicose veins with SONOVEIN® and breast fibroadenomas and thyroid nodules with Echopulse®.

Based in Malakoff, near Paris, our employees are constantly seeking innovation, combining high-level clinical research with the benefits of artificial intelligence. The varicose vein treatment market alone generates approximately 5 million procedures per year. It is therefore a dynamic market in which we are changing the paradigms by making non-invasive ultrasound therapy the new standard.

Exhibitors

American Institute of Ultrasound in Medicine
www.aium.org

The American Institute of Ultrasound in Medicine is a multidisciplinary professional medical association of more than 9,000 physicians, sonographers, scientists, students, and other healthcare professionals. The AIUM is dedicated to empowering and cultivating a global multidisciplinary community engaged in the use of medical ultrasound through raising awareness, education, sharing information, and research.

Bracco
www.bracco.com/en

Bracco is one of the world’s leaders in diagnostic imaging. The Bracco Suisse Research Centre was founded in 1989 in Geneva from the spin-off of a research team of The Battelle Institute. The Centre has been devoting its efforts with an efficient process-oriented approach and has achieved a track record of innovations in the ultrasound field. The Bracco Geneva site, which houses both the R&D and Manufacturing Units, represents a key asset for the Bracco Group and a reference point at international level.

Bracco Suisse SA employs more than 120 people with high expertise in contrast agents for ultrasound medical imaging. The R&D group work actively for extending the potential of ultrasound-responsive agent to molecular imaging and therapeutic applications. Also, software solutions are developed for blood perfusion quantification using contrast ultrasound and AI-based image interpretation and reconstruction.
Daxsonics Ultrasound Inc.
daxsonics.com

Daxsonics Ultrasound provides engineering services for emerging ultrasound technologies. We work in all stages of the life cycle providing a range of services including R&D, acoustic stack design, transducer design, electronics, software design, firmware design, and system integration. We can help overcome the barriers of developing novel ultrasound technology. We have experience designing and building high-frequency, miniaturized arrays, as well as complex, 1024-channel 2D arrays. Daxsonics is proud to be your ultrasound technology solution provider.

DONG IL TECHNOLOGY LTD.
www.dongiltech.co.kr

DIT Piezo ceramic Solution provides piezo ceramic materials and parts for final products of end-users in various industries with its own piezo ceramic technology.

Electronics & Innovation, Ltd.
eandiltd.com

Electronics & Innovation, (E&I) supports the vast and exciting developments in ultrasound research and production in a wide variety of applications. We have a proven track record of manufacturing robust RF amplifiers; known throughout the industry for their ruggedness and reliability.

E&I can provide a solution from Research to Production, benchtop to module. We have the knowledge and experience to help you with your application setup.

FasterCures, Milken Institute
milkeninstitute.org/centers/fastercures

FasterCures, a center of the Milken Institute, is working to build a system that is effective, efficient, and driven by a clear vision: patient needs above all else. We believe that transformative and life-saving science should be fully realized and deliver better treatments to the people who need them.
Focused Ultrasound Foundation (FUSF)
fusfoundation.org
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The Focused Ultrasound Foundation was created in 2006 to improve the lives of millions of people with serious medical disorders by accelerating the development and adoption of focused ultrasound.

Focused ultrasound is an early-stage, noninvasive therapeutic technology that is transforming the treatment of many medical disorders. Every day without it translates into unnecessary death, disability, and suffering for countless individuals.

Unfortunately, the evolution of a new therapeutic medical device from concept to standard of care can take decades. Complicated and inefficient, the process requires the interaction of many organizations with differing agendas and timelines. There are also numerous technology, economic, regulatory and reimbursement obstacles to overcome.

Decades is too long for patients and their families to wait for medical breakthroughs. If we can accelerate the adoption of focused ultrasound, we can save lives.

FUS Partners
fusfoundation.org/the-foundation/programs/fus-partners

FUS Partners is a program of the Focused Ultrasound Foundation that serves as a galvanizing force in facilitating the rapid acceleration of commercialization of focused ultrasound technology, speeding the transition from laboratory research to widespread adoption and utilization of the technology.

The program systematizes, formalizes, and coordinates certain activities of the Foundation to address the critical unmet needs of members of the focused ultrasound community, including fostering relationships and developing critical resources with respect to regulatory and reimbursement; corporate financing; training and credentialing; employee recruiting; strategic partnerships and technology transfer; industry advocacy; and intellectual property.
Exhibitors | continued

**G2G Consulting**  
www.g2gconsulting.com

G2G provides Government to Growth (G2G) strategies and executes them by providing comprehensive government affairs, public relations, and economic development services for businesses and non-profits. G2G’s primary focus is connecting innovators to government. We are the government relations firm for innovative ways to solve society’s biggest challenges.

**HistoSonics**  
www.histosonics.com

HistoSonics, a Minneapolis based medical technology company, is developing a novel non-invasive platform and new sonic beam therapy utilizing the science of histotripsy, a novel mechanism of action that uses focused acoustic energy to mechanically destroy and liquify targeted tissues at the cellular level with precision and control.

**IEEE Ultrasonics, Ferroelectrics, and Frequency Control Society (UFFC-S)**  
ieee-uffc.org

IEEE Ultrasonics, Ferroelectrics, and Frequency Control Society is an organization that promotes the advancement of the theory, technology, materials, and applications relating to the generation, transmission, and detection of ultrasonic waves and related phenomena; medical ultrasound, and associated technologies; ferroelectric, piezoelectric, and piezomagnetic materials; frequency generation and control, timing, and time coordination and distribution.

IEEE UFFC-S brings academics, industry professionals, researchers, and others involved in Ultrasonics, Ferroelectrics, and Frequency Control access to the industry’s technical information, networking opportunities, career development tools, and many other benefits exclusive to the Ultrasonics, Ferroelectrics, and Frequency Control Society.

**IMGT Co., Ltd**  
nanoimgt.com

IMGT Specializes in drug delivery system development paired with therapeutic focused ultrasound.

**Goal**  
Effective tumor therapy without the harmful side effects

**Core Competence**  
Specific targeting of anti cancer agents to tumor and the synergy effects when triggering by our very own therapeutic ultrasound device.
International Society for Therapeutic Ultrasound (ISTU)

istu.org

The International Society for Therapeutic Ultrasound (ISTU) is a non-profit organization founded in 2001 to increase and diffuse knowledge of therapeutic ultrasound to the scientific and medical community, and to facilitate the translation of therapeutic ultrasound techniques into the clinical area for the benefit of patients worldwide.

Korust Co., Ltd.

www.korust.com/eng

Korust Co., Ltd. is a Korean ultrasound company that manufactures HIFU devices.

Since 2012, Korust company has been committed to manufacturing innovative ultrasound devices.

We are the very first company to manufacture aesthetic HIFU devices for skin lifting and rejuvenation in Korea.

All of our products are CE certified and currently being exported to more than 25 countries worldwide.

Our latest product, RHINOS, is the HIFU device for treating severe nasal congestion caused by hypertrophy. Clinical trials have been done, and studies prove its effectiveness as a non-invasive method of lower turbinate hypertrophy reduction surgery.

RHINOS is currently in the process of getting a FDA approval.

For more information of our company and products, please visit our website at www.korust.com/eng.

PI (Physik Instrumente)

pi-usa.us

PI Ceramic is a global leader in the design and manufacture of piezoelectric transducers and piezoelectric components for life science and industrial ultrasound and dispensing applications. We provide high quality piezoelectric plates, blocks, ultrasonic transducers, piezo actuators, piezo ceramic motors, and a variety of high precision piezo mechanisms. Our highly controlled manufacturing processes allow for production of piezoelectric elements that are very clean, with extremely tight tolerances and minimum batch-to-batch variations. With decades of piezo transducer design and manufacture experience, PI Ceramic piezo products excel in a wide range of industrial and medical applications.
Profound Medical develops customizable, incision-free therapies which combine real-time Magnetic Resonance (“MR”) imaging, thermal ultrasound and closed-loop temperature feedback control for the radiation-free ablation of diseased tissue.

Profound is commercializing TULSA-PRO®, a technology that combines real-time MRI, robotically-driven transurethral ultrasound and closed-loop temperature feedback control. TULSA-PRO® is designed to provide customizable and predictable radiation-free ablation of a surgeon-defined prostate volume while actively protecting the urethra and rectum to help preserve the patient’s natural functional abilities. We believe TULSA-PRO® is demonstrating to be a flexible technology in customizable prostate ablation, including intermediate stage cancer, localized radio-recurrent cancer, retention and hematuria palliation in locally advanced prostate cancer, and the transition zone in large volume benign prostatic hyperplasia (BPH). TULSA-PRO® is CE marked and received 510(k) clearance from the U.S. Food and Drug Administration in August 2019.

Profound is also commercializing Sonalleve®, an innovative therapeutic platform that is CE marked for the treatment of uterine fibroids and palliative pain treatment of bone metastases. Sonalleve® has also been approved by the China Food and Drug Administration for the non-invasive treatment of uterine fibroids. The Company is in the early stages of exploring additional potential treatment markets for Sonalleve® where the technology has been shown to have clinical application, such as non-invasive ablation of abdominal cancers and hyperthermia for cancer therapy.

Sonic Concepts™ is a global leader in designing and delivering innovative therapeutic and focused ultrasound solutions, including the HIFUplex™ and NeuroFUS™ systems. Every day, researchers and organizations around the world use our best-in-class customizable products and turnkey ultrasonic therapy and imaging solutions to make medical breakthroughs and solve complex problems.
BrainSonix is a privately held company founded by Alexander Bystritsky, MD, PhD, an inventor and renowned neuro-psychiatrist and professor emeritus of psychiatry at UCLA. BrainSonix has developed a patented medical device platform utilizing Low Intensity Focused Ultrasound Pulsation (“LIFUP”) technology to non-invasively modulate neuronal activity without any harmful or irreversible effects on the brain and body.

Our technology has been used in several human clinical trials including open studies in Disorders of Consciousness after Brain Injury, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, and many others. Investigators using our device have won awards and grants from government agencies including NIMH, NIA, NINDS, VA; from professional societies such as American Society of Clinical Psychopharmacology, and from foundations such as One Mind and OCD Foundation.

The device was designed by company CTO Professor Mark Schafer (Drexel University), a preeminent engineer in the field of focused ultrasound, and current President of the IEEE Ultrasonics, Ferroelectrics and Frequency Control Society. The device is made using ISO compliant manufacturing, and has been extensively tested for electrical and MRI safety.

Inquiries should be directed to Alexander Bystritsky, MD, PhD, CEO of BrainSonix at 310-990-5644 or sasha@brainsonix.com

Carthera is a clinical-stage medtech company focused on developing innovative ultrasound-based medical devices to treat a wide range of brain disorders. The company is a spin-off from AP-HP Paris and Sorbonne University. Carthera leverages the inventions of Pr. Alexandre Carpentier, head neurosurgeon at AP-HP Sorbonne university, who has achieved worldwide recognition for his innovative developments in treating brain disorders. Carthera is developing the SonoCloud, an intracranial implant that temporarily opens the Blood-Brain Barrier (BBB). The device is currently in clinical trials in Europe and the United States.

Virginia Bio is the statewide, non-profit trade association for life sciences, developing and promoting the considerable scientific and economic impact of life sciences research, development and commercialization in Virginia. Virginia Bio also is an advocate for the biosciences ecosystem in Virginia with federal, state and local policy-makers. VA Bio is also the official state affiliate of the Biotechnology Industry Organization (BIO).
The global leader creating the next generation of patient care by realizing the therapeutic power of Focused Ultrasound.

Our Exablate Neuro platform provides treatment to patients with medication-refractory Essential Tremor and Parkinson’s Disease.

Insightec is committed to collaborating with healthcare professionals, scientists, and research organizations to promote and extend knowledge in the field of Focused Ultrasound technology.

Learn More at insightec.com
Expand your capabilities for Focused Ultrasound Research

Verasonics systems offer unparalleled flexibility with a wide variety of features and options

- HIFUplex™ Elite Focused Ultrasound research solutions
- Volume imaging solutions
- New transducer options
- Flexible architecture from 32 to 2048 channels
- Broad range of power output levels to meet the needs of Focused Ultrasound Research

To learn more, please visit us at FUS, visit our virtual booth at https://verasonics.com/fus2022-virtual-booth/ or contact us at sales@verasonics.com

Verasonics Inc.
11335 NE 122nd Way, Suite 100, Kirkland, WA 98034
www.verasonics.com  |  425.998.9836

www.verasonics.com
The Foundation’s Preclinical Awards Program supports technical and preclinical research to accelerate adoption of image-guided focused ultrasound.

For more information visit the For Researchers page at fusfoundation.org or contact Matt Eames, Director of Extramural Research, at meames@fusfoundation.org.

Funding Available for Focused Ultrasound Preclinical Research

Awards of approximately $100,000 for 1-year projects

Research award recipient Seung-Schik Yoo, PhD, MBA

The Foundation's Clinical Awards Program supports first-in-human and other innovative clinical trials involving the use of image-guided focused ultrasound to treat diseases.

Funding level determined on a case-by-case basis.

For more information visit the For Researchers page at fusfoundation.org or contact Matt Eames, Director of Extramural Research, at meames@fusfoundation.org.

Funding Available for Focused Ultrasound Clinical Studies

Research award recipient Nir Lipsman, PhD