5th International Symposium on Focused Ultrasound 2016

A field at the tipping point

Event Summary

August 28 - September 1, 2016

Bethesda North Marriott Hotel & Conference Center
Bethesda, Maryland, USA

Focused Ultrasound Foundation
10 years
advancing the field

Contents

Video presentations

To view the presentations, click on the bolded presenter names.

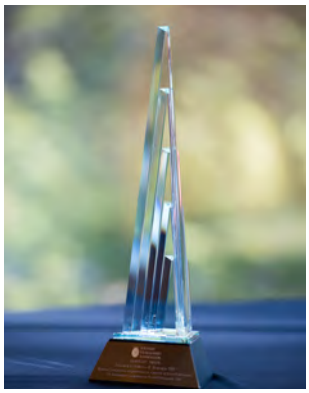
Welcome

Neal F. Kassell, MD

Founder and Chairman,
Focused Ultrasound Foundation

Professor of Neurosurgery,
University of Virginia,
Charlottesville, Virginia

Kassell welcomed the over 400 participants to the Symposium, which coincides with the Focused Ultrasound Foundation's 10th anniversary. In the past 10 years, the growth in the field has been astounding. When the Focused Ultrasound Foundation was established, there were only three mechanisms under investigation for focused ultrasound, compared with 18 today. A decade ago, there were only three clinical indications in various stages of preclinical and technical development; today there are more than 60. There were five manufacturers of focused ultrasound equipment, and now there are more than 30. There are also an increased number of treatment sites and patients treated with focused ultrasound. Kassell reminded participants of the theme of the Symposium, 'focused ultrasound, a field at the tipping point.' To cross over from being primarily a research enterprise, we need commercial success for indications with companies making profits. In order to achieve that, reimbursement for focused ultrasound indications is necessary. The founding of a clinical research society was proposed in order to move the clinical research forward. The goal of this meeting is to share information, create useful knowledge, and to forge and strengthen collaborations, partnerships, and friendships.



Honorary Presentations

Honorary President's Address

Jin Woo Chang, MD

Honorary President

Division of Stereotactic and
Functional Neurosurgery,
Brain Research Institute,
Yonsei University College of
Medicine, Seoul, Korea

Chang briefly discussed MRI-guided focused ultrasound for stereotactic and functional neurosurgery. Over the past few years he has used focused ultrasound to treat patients with essential tremor, obsessive compulsive disorder, and depression. Over time, Chang discovered that skull thickness and density played important roles in focused ultrasound treatment for brain disorders, and this helped to explain why the procedures worked in some patients and not others. There are many advantages of focused ultrasound over current surgical techniques used for neurosurgery, such as being less invasive and requiring only a short hospital stay. Chang hypothesizes that focused ultrasound holds great potential for a variety of indications in neurosurgery including neuropathic pain, epilepsy, psychiatric disorders, memory disorders, and new and innovative fields including blood-brain barrier (BBB) opening.

Ferenc Jolesz Memorial Award Presentation

Nathan McDannold

PhD, Department of Radiology,
Brigham & Women's Hospital,
Harvard Medical School,
Boston, Massachusetts

McDannold spoke about the use of low frequency ultrasound (230 KHz) in preclinical models for transcranial thermal ablation. Current limitations of this technique are that the treatment envelope is does not extend much beyond the central region of the brain, making treatment of peripheral areas and those near the skull difficult. One technique to expand the treatment envelope is to use a lower frequency to reduce skull heating. In nonhuman primate studies, a lower frequency decreases skull heating and aberration, and allows for wider beam steering but it also decreases focal heating and increases the risk for cavitation. McDannold next explored cavitation thresholds at this lower frequency. Results suggest that low frequency can increase the "treatment envelope" for focused ultrasound. Temperature/dose and histology suggest that lesions were created via thermal mechanisms and that cavitation level was controlled in real time. Thermally significant cavitation was detected in 75% of treated animals.

Keynote Speakers and Special Guests

Greg Simon, Executive Director of Vice President Biden's Cancer Moonshot Initiative, provided an update on the program's mandate, progress, and future. The Cancer Moonshot initiative includes an interagency Task Force and a blue ribbon panel comprised of 28 experts including the Foundation's own Dr. Neal Kassell, formed with the primary goal of reorganizing cancer care around the patient. The moonshot aims to restructure the culture of research, which has not changed in decades. Innovative ways of data sharing and processing, and creating new partnerships to enable better access to tools to achieve these goals have been proposed. New ways of reviewing and funding innovative technologies are also necessary. Simon concluded with a call to action to join in the moonshot and help achieve this shared goal of changing and improving the way cancer in treated.

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John Grisham was interviewed by CBS News Correspondent Chip Reid regarding the development and publication of Grisham's free book in support of the Foundation *The Tumor*. Grisham's interest in focused ultrasound grew after close family members experienced cancer. The stories in the book are based on the real stories of patient experiences with brain tumors. Grisham explained how the book has two endings to convey how scientific progress can truly alter someone's medical future.

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Philip Bourne, the first National Director for Data Science at the National Institutes of Health (NIH), presented on the promise, progress, and pitfalls of open science. There are different views on open science within the research community. The Cancer Moonshot is driving the push behind open science. The human genome project in 1996 laid the foundation for sharing data and changed the norms around data sharing in biomedical research. Genome research already has a culture of sharing, as in the NIH database of Genotype and Phenotype (dbGaP), and the NIH expects that in the future, researchers receiving NIH funding will allow access to their data as well.. Next, Bourne discussed the NIH Public Access Policy for publications. This initiative ensures public access to published results of all research funded by NIH since 2008. Recipients of NIH funds are required to submit final peer-reviewed journal manuscripts to PubMed Central (PMC) upon acceptance for publication. Papers must be accessible to the public on PMC no later than 12 months after publication. The Big Data Knowledge (BD2K) Initiative is currently under review and open for comment. Currently less than 50% of clinical trials are published within 30 months of completion. Bourne also discussed a notice of proposed rulemaking regarding clinical trials registration and results submission. This proposes to further implement statutory requirements on private and public sponsors to register and report results on phase 2, 3, and 4 trials. There is also a draft NIH policy on clinical trial information and dissemination that will extend publication requirements to all NIH-funded clinical trials.

Monday
August 29, 2016

Brain

Sessions on this day highlighted technical, preclinical and clinical results demonstrating the potential of focused ultrasound for treatment of a wide range of neurological disorders.

Movement Disorders – Clinical

Presentations highlighted clinical research for focused ultrasound treatment of movement disorders, including essential tremor, tremor in Parkinson's disease, and Parkinson's dyskinesia.

Jeff Elias from the University of Virginia (UVA) summarized recently published results (N Engl J Med. 2016 Aug 25;375(8):730-9) of an international, randomized, controlled trial of focused ultrasound thalamotomy for treatment of essential tremor. The FDA approved focused ultrasound thalamotomy for essential tremor on July 11, 2016. Inclusion criteria for the trial enabled patients with moderate-to-severe essential tremor that had not responded to at least two trials of medical therapy. Ninety-seven percent of patients completed the trial. Intraprocedural adjustments occurred in approximately 70% of procedures based on patient-feedback or MRI imaging during the procedure. The primary outcome was change in tremor score from baseline, with an average 40% decrease in tremor score 12 months after treatment. There was also a 60% reduction in disability score and large improvements in quality of life, including psychosocial scores. Adverse events in the thalamotomy group included gait disturbance in 36% of patients and paresthesias or numbness in 38%. The trial demonstrated that focused ultrasound improved hand tremor with side effects similar to traditional thalamotomy.

Menashe Zaaror from the Rambam Health Care Campus in Israel discussed treating Parkinson's disease and essential tremor with focused ultrasound. Between November 2013 and June 2016, 44 patients were treated with focused ultrasound, including 23 treated for essential tremor and 17 treated for Parkinson's disease. Despite widespread interest in the treatment, less than 50 patients have been treated to date due to a lack of reimbursement for the procedure and additional financial constraints. The aim of the study was to treat hand tremors, but they also treated the leg tremors as well. All patients, except one patient with Parkinson's disease, were tremor-free at the end of the procedure. At follow up at 6 months after the procedure tremor re-emerged in three patients with essential tremor, two with Parkinson's disease, two with both essential tremor and Parkinson's disease, and one with multiple system atrophy (MSA). In nine out of 12 patients with additional leg and/or jaw tremor, changing the target to the ventral intermediate (VIM) nucleus somatotopic representation successfully stopped the tremor. A patient with eye blinking also had eye blinking cessation. In all except two cases, the recurred tremor was much less disabling than before treatment. Forty-two of the 44 patients were satisfied with the procedure. During the procedure, if incomplete tremor control was not achieved, the target was incrementally adjusted in steps of 0.1 to 0.5 mm in accordance with the VIM somatotopic representation map. This trial demonstrated the importance of selecting patients with a skull density ratio of greater than 0.35; one should also identify tremor components to target (in accordance to the somatotopic representation of the ventralis intermedius nucleus of the thalamus). Future studies will include thalamotomy in the VIM nucleus for tremor in patients with multiple sclerosis, treating the same surgical targets as those used for deep brain stimulation to improve treatment for Parkinson's disease and dystonia, and focused ultrasound to treat patients with psychiatric disorders.

Aaron Bond from UVA presented results from a sham-controlled trial investigating transcranial MR-guided focused ultrasound thalamotomy for the treatment of tremor dominant, Parkinson's disease. The primary outcome measures were safety and improvement in tremor score at 3 months. Secondary endpoints included UPDRS motor scores at 3 months and 1 year, and CRST disability scores. There were 53 patients screened for eligibility, and 27 were eligible. Fourteen focused ultrasound (FUS)-treated patients and five sham-treated patients completed the 1-year assessment. The treatment group had a clinically and statistically significant 53% reduction in on-medication CRST A&B hand score at 3 months versus 17% in the sham group. There was a non-significant improvement in UPDRS motor score in the treated group at 3 months. There was a statistically significant tremor improvement in patients that were treated at a more anterior distance from the posterior commissure. There was a notable placebo effect, which is typical in patients with Parkinson's disease. Overall, tremor improvement was sustained at 1 year.

Jin Woo Chang from Yonsei University College of Medicine in Korea presented data from a feasibility study on unilateral lesioning of the globus pallidus internus (GPi) with FUS for the treatment of dyskinesia in patients with Parkinson's disease. The study included eight patients with medically refractory Parkinson's disease and followed patients for up to 1 year; one patient was excluded due to psychiatric comorbidities. UPDRS part III scores (on state) improved at 1-year: a 35% reduction for on state and 52% reduction for off state. Overall, focused ultrasound-treated patients demonstrated excellent motor outcomes. However, there were difficulties in achieving sufficient volume for thermal lesioning of the GPi as compared with the previous experience in patients with essential tremor.

Jonathon Parker from Stanford University discussed results from a cost-effectiveness analysis on FUS for essential tremor in comparison with deep brain stimulation (DBS) and stereotactic radiosurgery. While phase III data supports the safety and efficacy of FUS for reducing tremor and improving quality of life, the relative cost-effectiveness of the available modalities is unknown. In the setting of limited healthcare resources, reducing procedural costs is critical to improve access to the most effective treatment and reduce societal costs of treatment and impaired quality of life. A meta-analysis paradigm was developed for the comparison. Utility scores represent the percent improvement in activities of daily living and utility parameters from each study were pooled/weighted according to the number of subjects to generate a singular value for each modality. FUS exhibited superior utility compared with DBS and stereotactic radiosurgery. FUS also maintained a utility advantage after correction for complications. Compared with the other modalities, FUS costs are predicted to be lower than DBS and comparable to stereotactic radiosurgery.

Vibhor Krishna from The Ohio State University presented initial results on tractography-based MRI analysis methods for the identification of the ventral intermediate nucleus (VIM), which is not visible with conventional MRI. Currently there are formulaic methods and physiology-based adjustments, special MRI sequences, and atlas-based localization (CRAVE) methods. Tractography-based VIM targeting using the dentatorubrothalamic tract is an imaging marker that has been used in DBS and FUS. The goal was to obtain high anatomical accuracy. Tensor calculations were streamlined with StealthViz for low sensitivity, but high specificity and integrated with a surgical targeting platform (Framelink). This methodology was used to treat eight patients with essential tremor. Intraoperative efficacy was defined as a 10 second therapeutic sonication (> 55°C) that resulted in a >50% tremor reduction. The short-term results were promising. There was a more than 50% reduction in CRST at 1 month with no motor or sensory side effects with optimized surgical time. The long-term durability is unknown and further research will explore motor outcomes and side-effect profiles.

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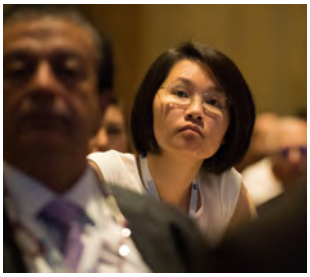
Panel Discussion: Movement Disorders

Panel Moderator: Neal Kassell. Panelists: J.W. Chang, W.J. Elias, P. Fishman, V. Krishna, and M. Zaaroor.

The panel discussed the following topics:



1. **How to optimize the selection of patients for FUS versus DBS?**
   The clinical experience has been that patients are requesting FUS. A patient with asymmetrical essential tremor is a good candidate, since FUS is only applied unilaterally at this time and DBS is proven effective bilaterally. The decisions are often patient-driven. It is nice to have an additional option as there are few alternatives to DBS. Another consideration is patient profession; for someone who needs their hands, a titratable option such as DBS is preferred. Age is also important and younger patients (< 50 years of age) are better candidates for DBS. The consensus of the panel was that FUS was an alternative to offer patients considering DBS.
2. **Is it possible to carry out a randomized controlled trial of FUS vs. DBS?**
   It seems unlikely that such a trial is possible. In other trials that had a surgical arm (or invasive procedure) it has been difficult to get patients willing to participate. Many patients had issues with leaving such a big decision up to chance. However, the results of a comparative trial would be greatly helpful to the field. It may also be unfair to compare the two procedures at this stage of development. A worldwide registry would be a better way to study the comparative effectiveness between FUS and DBS.
3. **Is it possible to re-treat patients that have symptoms of recurrence?**
   The first step is to examine the efficacy of the treatment, considering targeting of the lesion and temperature, etc. The clinical experience has been that the tremor stops once a therapeutic temperature is reached. The technology does lend itself to retreatment in patients with recurrence. In addition, DBS could be appropriate for retreatment.

4. **Would you consider treating patients bilaterally?**
   There is strong literature on bilateral treatment in DBS. The panel expressed concern about safety using FUS for bilateral treatment. It is unknown at this time if FUS can be optimized to make large lesions. We need clinical trial data to understand this better. However, other panelists disagreed with the size approach. Lesion size does not predict outcome, and an alternative is to think about how small of a lesion size could still be effective. The point was stressed again that carefully conducted clinical trials could be done to answer the bilateral question.

   One issue is that the mechanism behind the success of FUS for essential tremor is still not well-understood. More research will help to understand how to use the technology. One advantage with FUS over DBS is that the clinician can follow the tractography, and this is not possible with DBS.
5. **Is it possible to use FUS for target verification in multiple sclerosis (MS)-related tremor?**
   MS tremor may be more difficult, and there have been mixed results with DBS in these patients. Patient selection is also extremely difficult in these patients.
6. **Is it possible to use FUS for the treatment of dystonia?**
   The panelists were more positive about this application. Stereotactic procedures show good efficacy in dystonia, but DBS has been abandoned. The globus pallidus is a good target for FUS. One issue is the need for bilateral treatment, which will require safety studies. If there is clinical efficacy of bilateral lesioning in Parkinson's disease, then consider dystonia as a possible indication.
7. **What is your technical wishlist to make these treatments relatively faster and safer?**
   - Pretreatment visualization of positioning of the transducer to minimize treatment time
   - The ability to block some of the transducer elements to better focus the treatment to the desired location

- The ability to stop shaving patient's heads for the treatment, since this deters some patients from the procedure
- The ability to map the targets via neuromodulation prior to treatment
- The ability to contour and shape the ablation beyond just the elliptical shape available now
- Enabling an outpatient procedure where the patient returns home the same day

In summary, the expectation is that two years from now there will be a registry available to collect data. Patients will have the ability to be re-treated, neuromodulation will be available, and perhaps treatment will be available for patients with dystonia.

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Parkinson's Disease – Preclinical

Presentations highlighted preclinical research in Parkinson's disease using FUS plus microbubbles to induce BBB opening as a mechanism to enhance delivery of potential therapeutics.

Brian Mead from UVA discussed targeted delivery of brain-penetrating non-viral glial-cell-derived neurotrophic factor (GDNF) gene vectors to the striatum for the treatment of neurodegeneration in Parkinson's disease. Currently, clinical gene therapy trials for Parkinson's disease have shown safety, but not efficacy due to poor delivery to the target. The delivery particle is a polyethylenimine-polyethylene glycol brain-penetrating nanoparticle (BPN). Using the 6-OHDA model of Parkinson's disease, FUS was used in combination with microbubbles to open the BBB and enable delivery of GDNF-BPN into the brain. FUS-enhanced delivery of GDNF-BPN increased GDNF protein levels approximately 10-fold in the treated striatum, which persisted 12 weeks after the initial treatment. Additionally, GDNF-BPN restored locomotor function and dopaminergic neuron density.

Shutao Wang from Columbia University discussed FUS enhanced delivery of genes in a mouse model (MPTP) of Parkinson's disease and the potential for neurorestoration of dopaminergic neurons. They used an AAV-GDNF (AAV1-CAG-GFP-GDNF) vector. Dopaminergic neuron projections were significantly higher with FUS plus AAV treatment. There was also increased dopaminergic neuron terminal density in the striatum after combined treatment and improved behavioral response (amphetamine rotational response) Future studies will focus on long-term effects of gene therapy and the utilization of large animal models.

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Alzheimer's Disease

Presentations highlighted preclinical research investigating FUS as a treatment for Alzheimer's disease. Several therapeutic options were explored, from BBB opening alone (using FUS and microbubbles) to treatment with antibodies and neurotrophic factors.

Kullervo Hynynen and colleagues from Sunnybrook Health Sciences Centre have extensively studied FUS for the treatment of Alzheimer's disease in animal models and reviewed the recent work from his laboratory. Mice that underwent opening of the BBB via FUS and microbubbles showed reduced plaque load and improved working memory performance (Y-maze). One of the mechanisms behind this effect is the generation of new neurons. In a subsequent study they demonstrated that BBB opening was necessary for the generation of new neurons. Furthermore, they have found two types of particle leakage from the BBB into the brain after FUS: fast and slow. Older Alzheimer's mice showed predominantly slow leakage compared to normal mice.

Gerhard Leinenga from the Queensland Brain Institute discussed scanning FUS for the disruption of the BBB in a mouse model of Alzheimer's disease to target extracellular amyloid-beta (Aβ). In a mouse model of Alzheimer's disease treated with weekly scanning ultrasound (FUS applied to the whole-brain sequentially), there was a 50% reduction in the number and size of plaques and restoration of memory

function in the treated mice. A proposed mechanism is that microglia are altered by blood-borne factors that enter the brain after the BBB opening. This treatment shows no change in neuronal excitability and prevents age-related reductions in hippocampal CA1 dendritic structure in wild-type mice. In summary, in addition to ameliorating the Aβ pathology of Alzheimer's disease, repeated whole-brain FUS may slow down morphological changes in neurons associated with progressive aging.

Jürgen Gotz of the Queensland Brain Institute spoke on using scanning FUS for the treatment of proteinopathies in Alzheimer's disease. A model of Alzheimer's disease that overexpresses intracellular tau (pR5) was used in these experiments. RN2N single-chain variable fragments (scFvs) can recognize 2N tau isoforms. RN2N antibody treatment in combination with scanning ultrasound reduces anxiety-like behavior in pR5 tau transgenic mice. RN2N in combination with scanning ultrasound significantly reduces phosphorylated tau levels in the amygdala. Mechanistic studies are ongoing, but RN2N is efficiently taken up by neurons in brains treated with scanning FUS.

Marilena Karakatsani from Columbia University discussed targeting the nigrostriatal pathway with FUS to facilitate drug delivery of a neurotrophic factor (neurturin (NTN)) in a model of Parkinson's disease. Previous research demonstrated that NTN administration after focused ultrasound-induced BBB opening initiated the downstream signaling pathway. Single and triple administration of NTN restored degenerated neurons at the substantia nigra and caudate-putamen regions. The groups that received NTN had a greater number of cells in the ipsilateral side from treatment. There was restoration at the dendritic site of the substantia nigra and at the terminal site of the caudate region. Multiple treatments show potential in restoring dopaminergic neurons.

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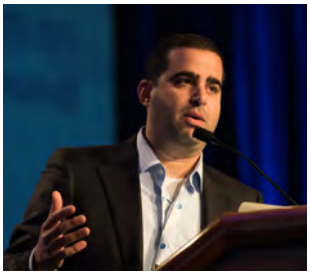
Psychosurgery

Presentations highlighted FUS for psychosurgery applications including the first clinical experience treating obsessive compulsive disorder.

Jin Woo Chang from Yonsei University College of Medicine presented data on the use of bilateral lesioning with FUS for the treatment of obsessive compulsive disorder. Efficacy was measured via Yale-Brown Obsessive Compulsive Score (Y-BOCS) change from baseline. FUS was used to produce bilateral lesions in the anterior limb capsule in 12 patients. Eleven out of 12 patients responded to the treatment. They also found decreased glucose metabolism after lesioning in the caudate nucleus, inferior frontal region, and the orbitofrontal cortex. Full neurocognitive functional testing showed no differences before and after treatment. One year after treatment the Y-BOCS score continued to decrease. Skull density and volume may present challenges in selecting future patients.



Nir Lipsman from the Sunnybrook Health Sciences Centre discussed the importance of FUS for psychosurgery. Throughout history, various surgical techniques were attempted for treatment of mental illness. The development of stereotactic surgery allowed precise targeting of brain regions with millimeter accuracy. Psychiatric disease drives neurosurgical innovation. There has been recent scrutiny of newer technologies such as DBS and gamma ventral capsulotomy. It is a critical time for neuromodulation in psychiatry, and systematic exploration at a deeper level will be necessary to evaluate new technologies. The next steps will determine the viability of psychiatric neurosurgery. There are three proposed directions for FUS to advance the field of psychiatric neurosurgery. First, FUS may be used for precise lesioning in neuropsychiatric disease. Second, FUS may have the ability to modulate the brain in a noninvasive and non-permanent way though the literature here is not well defined. Finally, FUS-induced BBB opening could enhance the delivery of treatment agents, particularly for depression and anxiety.

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Epilepsy

Nathan Fountain from UVA presented the trial design for an upcoming clinical trial on the use of focused ultrasound for treating subcortical epilepsy (FUSE). Seizures are caused by hyperexcitability of neurons. Subcortical epilepsy has an epileptic focus that is not in the cortex, and traditional surgical techniques require transversing the brain to reach the central sulcus. For this reason, surgery is usually reserved for very severe cases, or avoided entirely. FUS is appealing as it is minimally invasive, allows focal application of energy, and is ideal for treating central brain lesions. This trial will focus on lesioning of deep brain targets. The FUSE study is a planned open label safety and feasibility pilot study with a targeted enrollment of 15 patients with subcortical epilepsy. The targeted lesions will be hypothalamic hamartoma, DNET, periventricular nodular heterotopia, focal 'cortical' dysplasia, and tuberous sclerosis. The trial will be a single MRI-guided FUS treatment; a targeting model will be created in advance. The treatment will use a low temperature to visually confirm temperature change to the target followed by the creation of a high temperature lesion. There are strict patient inclusion/exclusion criteria including a minimum of three focal seizures per month, currently taking two antiepileptic drugs, and previously failed two antiepileptic drugs with a lesion target that is within the treatment envelope. FUS has a high potential to provide effective ablation of subcortical epileptic lesions. Future developments will likely allow a larger treatment envelope. If FUS is as low risk as expected, it could shift the risk-benefit ratio away from intracranial monitoring towards empiric therapy.

Blood-Brain Barrier Opening

Presentations highlighted preclinical results with a variety of potential clinical applications using FUS in combination with microbubbles for safe and temporary opening of the BBB to facilitate delivery of promising therapeutics.

Paul Fishman from the University of Maryland presented results demonstrating a new technique to enhance focused ultrasound-mediated delivery of stem cells to the brain. During normal FUS BBB opening, there is only a small fraction of injected human neuronal progenitor cells (NPCs) that enter the brain following intra-carotid injection in rats. Human NPCs in culture will engulf super paramagnetic iron oxide nanoparticles (SPION) with no change in viability or differentiation. In animal experiments, these particles could label cells and allow them to be tracked by MRI or manipulated by magnetic gradients. Ongoing preclinical trials use a powerful magnet placed by the head after focused ultrasound-mediated BBB opening to increase the likelihood of SPION-loaded stem cells entering the brain from the blood. Results show that a magnet can dramatically increase the fraction of SPION-loaded stem cells that enter the brain after an IV injection compared to non-magnetic particles.

Carlos Sierra from Columbia University presented preclinical results using lipid fluorescent microbubbles in combination with FUS for targeted drug delivery. The study objectives were to develop lipid fluorescent microbubbles, study the feasibility and safety of the fluorescent microbubbles as a vehicle for targeted drug delivery, and define the cavitation dose thresholds for assessing successful drug delivery. Microbubbles were labelled with the fluorophore 5-dodecanoylaminfluorescein. Fluorescent microbubbles can be used to open the BBB from 450 to 750 kPa. Lipid microbubbles could be safely used as a vector for targeted brain drug delivery at pressures up to 600 kPa, reducing systemic exposure. Cavitation dose thresholds for assessing successful drug delivery were defined. Cavitation dose above these thresholds led to significant fluorescent enhancement in the sonicated regions. The fluorescent particle delivery was successful in the sonicated area and there was diffusion to the untreated side through the fibers of the corpus callosum and the cingulum. Future work will focus on safety evaluations at pressures higher than 600 kPa and also study the mechanism of fluorescent particle diffusion from the sonicated side to the untreated side.

Muna Aryal from Brigham & Women's Hospital discussed ultrasound-mediated delivery of gadolinium and fluorescently-labelled liposomes through the BBB. Liposomes with gadolinium and fluorescence (Rhodamine) labelling were developed. FUS was used to deliver the liposomes across the BBB. The researchers measured whether the liposomes extravasated in a size-dependent manner and whether the acoustic emissions were size-dependent. Sonication increased the extravasation of liposomes. Liposomes as large as 150 nm diffused across the brain parenchyma. Liposome accumulation was not size-dependent. Acoustic emissions from cavitation were not size-dependent when liposomes were injected before sonication.

Zsofia Kovacs from the NIH discussed the sterile inflammatory response in the brain following exposure to low-intensity-pulsed FUS and microbubble (Optison®) infusion. The sterile inflammatory response can result in cell stress and the initiation of stress responses. A proteomic heat map was generated and HSP-70, IL-1a, IL-1b, IL-18, and TNF-α were increased following pulsed FUS, suggesting a pro-i nflammatory response. Histological analysis confirmed the inflammatory response including DNA damage, astrogliosis, and microglial and endothelial cell activation. Cells that were positive for TUNEL staining were mostly neurons. An additional study used fluorescently labelled systemic CD68+ macrophages, and the infiltration of these cells into treated tissue suggests that an innate immune response is induced. There was no evidence of microhemorrhages within the parenchyma.

Zsofia Kovacs also presented on the long-term effects of BBB opening with pulsed FUS and microbubbles (Optison®). Rats were sonicated once or six times, and monitored for 7 or 13 months. There was some evidence of microhemorrhage on MRI 2 weeks after sonication. A single sonication caused structural injury or white matter abnormalities in nearly 50% of the animals. Multiple sonications resulted in increased neuronal damage and associated atrophy with ventriculomegaly, meningeal thickening, astrogliosis, and microglia activation 1 week after the last sonication. Fifty percent of the rats had persistent BBB opening 1 week after the 6th sonication, and BrdU+ cells indicated that the stimulation of neurogenesis was secondary to repeated SIR episodes in the parenchyma. There was evidence of microglia activation and ongoing inflammation in sonicated regions. The investigation of the long-term effects of FUS in combination with microbubbles is crucial prior to planning clinical trials based on multiple courses of BBB opening.

David Hersh from the University of Maryland discussed research exploring how pulsed ultrasound non-destructively expands the extracellular and perivascular spaces of the brain. Brain extracellular space takes up about 20% of total brain volume. In vitro research showed that pulsed ultrasound expands interstitial tissue. Pulsed ultrasound also caused non-uniform displacement induced shear forces and the resulting strain creates structural effects and enhanced tissue permeability. The group has designed an in vivo rat study to look at whether pulsed ultrasound can enhance the intracerebral distribution of nanoparticles by affecting the pore size of the extracellular space. Non-adhesive nanoparticles were injected and tracked with high-resolution microscopy. Preliminary results will be obtained soon.

Brain – Technical

There were a variety of topics covered during the technical brain session. Most focused on methods to improve the use of FUS for treating human patients.

Henrik Odeen from the University of Utah presented 3D volumetric MR temperature imaging (MRTI) for use in clinical-FUS systems. Experiments were performed using a gel-filled ex vivo human skull. 3D temperature images produced by the method correlated well to conventional 2D thermometry images. 3D MRTI detected higher far-field temperature changes than fiber-optic probes. 3D GRE (Gradient Recalled Echo) and EPI (Echo Planar Imaging) are useful research tools and potentially useful clinical tools. 3D GRE achieves accurate focal spot localization with a single sonication, providing a time-saving alternative to multiple sonications required with 2D MRTI.

Kim Butts Pauly from Stanford University presented a comparison of multi-echo MRTI and single echo MRTI for the treatment of essential tremor. Current methods are time-consuming and are artifact prone. To maximize the signal-to-noise ratio, a low bandwidth is used, which is prone to spatial shift artifacts. A multi-echo sequence is now available, uses multiple high bandwidth acquisitions, and combines them into one temperature map. Using a higher bandwidth reduces the spatial shift. Data from six patients were analyzed. Multi-echo improved signal-to-noise ratio, significantly reduced spatial shifts, and reduced artifacts as compared to single echo when phase encode S/I. In conclusion, multi-echo can save time, achieve better resolution, and reduce spatial shifts to ˂0.33 mm.

Sumeeth Jonathan from Vanderbilt University presented high-resolution whole-brain MR thermometry with a 3D stack-of-stars EPI pulse sequence. The Golden Angle stack-of-stars EPI acquisition was used to increase volume coverage. Temperature reconstruction was performed and results suggest that 3D Stack-of-Stars EPI permits high-resolution MR thermometry with either SENSE or k-space hybrid temperature reconstruction. The Golden Angle radial ordering enables flexible adjustment of frame rate and sliding window reconstruction. For example, higher frame rates for monitoring the focus and lower frame rates for near/far-field safety monitoring. EPI slice sampling enables flexible adjustment of volume coverage. Limitations include low pixel bandwidth in slice dimension.

Costas Arvanitis from the Georgia Institute of Technology discussed ultrafast and sensitive volumetric passive acoustic mapping. Passive acoustic mapping has the potential to combine signaling information from the diverging spherical pressure waves radiated by microbubbles. This method would allow the combination of this information within a single image and with very high sensitivity and specificity. There are three types of passive acoustic mapping: time domain, frequency domain, and angular spectrum. The researchers used simulations to look at these three types for 2D passive acoustic mapping. The angular spectrum was a very fast and sensitive approach that can be used to characterize the type of oscillations (stable versus inertial), localize cavitation activity, and modulate the desired interaction non-invasively.

Dennis Parker from the University of Utah discussed tissue stiffness imaging with interleaved multiple-point MR-acoustic radiation forced imaging (ARFI). MR-ARFI has been used for focus localization and to detect changes in tissue stiffness. There are different methods of ARFI: spin echo and gradient echo (GRE) as well as 2D and 3D. This research group is focused on 3D MR-ARFI. For single versus multipoint MR-ARFI there are trade-offs for speed versus heating. Experiments were conducted in gel phantoms and excised pig brains. 3D multipoint MR-ARFI demonstrates feasible multiple interleaved volume displacement measurements and greatly increases displacement to noise ratio, with an acquisition time of 40 to 90 seconds. Further optimization will increase efficiency.

Guillaume Maimbourg from the Institut Langevin discussed the binary localization (inside or outside of the skull) of cavitation activity based on harmonic content for transcranial therapy. Cavitation mapping can be used for localization. It is efficient for 3D localization, but it requires more than three passive cavitation detectors and is costly. The group has created an in vitro setup for mimicking inside/outside the skull cavitation. Ultraharmonic ratios were measured every 26 milliseconds during about 6 seconds for cavitation induced in calf brain by 6MPa ultrasound. Binary localization is efficient in vitro and requires only one passive cavitation detector at a low cost. Further research will assess this system for use in vivo.

Kim Butts Pauly from Stanford University presented on the temperature versus power curve during FUS and the correlation with lesion localization. Sometimes the temperature decreases as we increase power. The purpose of their study was to investigate focal spot movement away from the thermometry scan plane, as an explanation for the lower-than-expected temperature rise. Fourteen patients were treated with targets in the ACPC plane. Temperature images were obtained in the axial plane, the number of sonications after the inflection point were counted, and the number below the expected temperature were recorded. Immediately post-treatment the top and bottom images of Zone 2 were

obtained in the sagittal plane, and the distance to the ACPC plane was measured. The top edge is further away from the ACPC plane with more sonications, and the bottom edge is relatively constant with the ACPC plane. The data was consistent with the lesion moving towards the transducer, away from the target. As the acoustic parameters change, absorption increases. Implications for clinical treatment suggest that we need better thermometry information. Volumetric thermometry is necessary for improved temperature mapping.

Dong-Guk Paeng from UVA and the FUS Foundation presented histological results as a function of thermal dose in pig brain. A 3-day survival pig study was used to investigate the brain tissue damage caused by lower temperatures (46~52°C) for longer (~ 3 min) pulsed sonication and to confirm it in MR images and histology as a function of thermal dose. The current approach to brain treatment is to use a peak temperature over 55 °C for tens of seconds using a continuous acoustic wave. The pig brain tissue was damaged over 101 cumulative equivalent minutes (CEM43) with lower temperature (46~50°C) and confirmed both in MR coronal images and histology 3 days after sonication, but below 101 cumulative equivalent minutes there was some uncertainty.

John Snell of the FUS Foundation presented a visualization tool for transcranial FUS that is in development. The tool will allow graphical visualization of the geometry of transcranial FUS. The tool can be shifted in any plane due to it being in 3D. It will also allow element raytracing, and can be used to trace a refraction path through the inner and outer surface of the skull. The 3D maps take into account only the incident angles on the outside of the skull, and do not account for other issues like absorption rates. The tool can be used to estimate efficiency based on the chosen critical angle. The model also allows visualization of the stereotactic frame and potential collision points with the transducer. The tool will be released as open source software within the next few months.

James Drake, presenting on behalf of Thomas Looi, discussed the development of a FUS system for pediatric neurological treatments. Transcranial systems are quite large. An MRI-compatible incubator is already available, and the team wanted to develop a similar system for FUS given the constraints of the incubator and patient size. There are two primary clinical indications motivating the design of this system. One is intraventricular hemorrhage, with the goal to investigate if MR-guided FUS can treat and dissolve these clots. There is currently no other direct treatment method. The second indication is medically refractory epilepsy; the team plans to initially select targets that can be surgically resected such as hypothalamic hamartomas. This resulted in the design of a HIFU system for pediatric operation (HOPE). The team designed and developed a FUS robot with neuro-interventional coil for high-intensity FUS (HIFU) treatment along with a software platform for target planning and selection. The system allows for thermal ablation, hyperthermia and cavitation-based therapy. It also has a larger workspace while allowing integrated incubator usage. The system is physically complete and will go into testing in the fall of 2017.

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Panel Discussion: Brain Technology

Panel Moderators: J. Aubry and J. Snell. Panelists: K. Butts Pauly, C. Cain, K. Hynynen, D. Parker, and E. Zadicario.

The panel discussed their opinions on the following topics:

1. **What are the technical issues remaining today??**
   The treatment envelope is very important. Another issue is predictability, as it is still very difficult to achieve the desired temperature and target. More data will be helpful in understanding this. The efficiency of FUS is variable, and the treatment envelope may be specific to each patient.

   The transducer itself could be optimized. An interesting idea is that different transducer shapes could be created for different purposes. A single transducer for all brain treatments may not be the best strategy. Skull size and thickness are important. The utility of the skull density ratio was

discussed by the panel. The skull density ratio is useful for predicting if the beam focusing will be effective, but cannot predict the amount of energy that will enter the skull. Thermal dose may be another way to optimize the system.

2. **MRI guidance will be necessary in the short-term, but will it be possible to perform FUS outside of MRI?** For histotripsy, it may be possible as there is only the need to estimate the location of the bubble cloud. For BBB opening, the goal is to eventually perform it outside of the MRI. There may be methods to use prior localization data to predict future treatments, but for many indications it will still be necessary to use a stereotactic frame and MRI will be necessary to visualize the area of treatment prior to FUS.
3. **How close are we to being able to do real-time treatment monitoring?** 3D thermometry in real-time is necessary. There can be delayed heating from bone absorption, which is released into the brain tissue. Again, the more data we have, the better we can predict future treatments. The panel mentioned again that the ability to disable parts of the array, so that off-target portions of the skull are not heated, should be considered.
4. **Wish list?**
   - Treatment predictability
   - The ability to reach the same temperature every time
   - Advances in imaging: 3D thermometry, intraoperative tissue viability imaging, etc.
   - Advances to improve patient comfort, discontinue the need for a stereotactic frame and head shaving.

Neuromodulation

Presentations highlighted preliminary research in both humans and preclinical models demonstrating FUS's ability to induce neuromodulation, including within the somatosensory and primary visual cortices.

Wonhye Lee from Harvard Medical School presented on simultaneous stimulation of the somatosensory cortices using transcranial FUS in human patients. Previous research demonstrated that various types of tactile sensations were elicited by stimulating the human primary somatosensory cortex. Next, the team assessed the types of tactile sensations elicited by FUS stimulation of the separate somatosensory cortices in 10 patients. Sensation could be elicited by simultaneously stimulating the primary and secondary as well as by stimulating the secondary somatosensory cortex alone. Stimulation of both cortices elicited various tactile sensations. Stimulation of the secondary somatosensory alone induced tactile sensations, that were similar to those elicited by electrical cortical stimulation. The simultaneous stimulation of the primary and secondary cortices is feasible, and has not been possible with other modalities.

Wonhye Lee also presented the use of transcranial FUS for stimulation of the primary visual cortex in humans. The researchers used FUS in combination with fMRI and cortical EEG to examine brain areas activated by stimulation of the VI in conscious humans (N=19) during simultaneous acquisition of fMRI. FUS activated the sonicated brain area of VI as demonstrated with fMRI, and concurrently elicited the associated efferent sensory perception in the form of a phosphene. Simultaneous fMRI acquisition in conscious humans revealed that FUS activates the brain network of regions involved in visual and higher-order cognitive processing. Successful stimulation of the VI was also supported by the presence of evoked EEG potentials.

Charles Caskey from Vanderbilt University presented on FUS modulated visual search performance in nonhuman primates. The objective was to determine whether FUS can be used to modulate brain circuitry of the frontal eye field in nonhuman primates (N=2). FUS was applied to the frontal eye field during a behavioral task Gaze behavior and event-related potentials were measures. The researchers found a robust spatially selective slowing of a saccade in one subject at 425 kPa, and the visual cortex EEG was

reduced with high pressure. There were no elicited responses or detectable changes in accuracy. Future work will improve the accuracy of beam placement, and perform observations in the fMRI.

Christian Aurup from Columbia University discussed ultrasound-mediated modulation of motor and associated EEG responses in mice in vivo. The goal of the study was to demonstrate that FUS targeted to cortical structures could elicit paired motor responses. FUS could also modulate anxiety-related subcortical structures by eliciting ocular responses. The somatosensory area was stimulated to elicit responses in the contralateral side. Results showed that FUS in the MHz-range could safely modulate neuronal activity in cortical regions of the mouse brain. There was no evidence of red blood cell extravasation. The MHz-range allows for smaller focal size and greater anatomical specificity and higher pressures elicit responses more readily. Ongoing work will optimize modulation and evaluate possible mechanisms of action.

Nick Todd from Harvard Medical School discussed neuromodulation via the targeted delivery of neurotransmitter chemicals. Stimulation activation experiments were carried out in rats, using focused ultrasound-induced BBB opening followed by a bolus injection of GABA. fMRI was used to measure activation. Preliminary results from two rats have been obtained. With BBB opening, there was a possible suppression of effects that are dependent on FUS power without GABA. With GABA injection and BBB opening, initial results suggest that GABA has a significant suppression effect, but more animals are needed for statistical analysis.

Brain Summary

Tim Meakem of the FUS Foundation summarized where the Foundation sees the field headed over the next 2 years. Expectations for clinical advances include:

- Essential tremor
  - Repeatable treatment demonstrated
  - Bilateral treatment demonstrated
  - Patient selection guidelines in place
  - Skull-related limitations reduced or eliminated
- Parkinson's disease
  - Tremor dominant – treatment in practice
  - Dyskinesia – pilot study completed
- Dystonia treatment and multiple sclerosis tremor
  - Pilot studies in progress
- Treatment of depression and obsessive compulsive disorder:
  - Pilot studies completed
- Epilepsy
  - Pilot trials completed for hamartoma, anterior nucleus of the thalamus, and temporal lobe.
- Brain tumors
  - Pilot trials in progress for treatment via thermal ablation, microbubble-enhanced ablation, histotripsy, and sonodynamic therapy
  - Pilot trials in progress for treatment via drug therapy or immunotherapy in combination with FUS
- Alzheimer's disease
  - Pilot trials in progress for BBB opening alone and with drug delivery
- Neuropathic pain
  - Pilot trial completed

There were also several technical and preclinical goals for the next Symposium.

- Expansion of the treatment envelope to include the entire cranium, by one or more of the following mechanisms:
  - Thermal
  - Microbubble-enhanced
  - Histotripsy
- Non-thermal targeting with ARFI or another technique
- The ability to treat the entire lesion with conformal volumetric techniques
- Bubble cloud imaging
- Real-time treatment monitoring

Tuesday
August 30, 2016

Cancer

Sessions on this day highlighted technical, preclinical and clinical results demonstrating the potential of FUS for treatment of cancer.

Brain Tumors

Presentations highlighted the use of FUS in the treatment of brain tumors. Human clinical trials using FUS and microbubbles to open the BBB and enhance delivery of chemotherapy have recently begun. Preclinical results demonstrated several methods by which FUS could treat brain tumors: BBB opening, mechanical ablation and sonodynamic therapy.

Nir Lipsman presented a summary of the first pilot clinical study using MR-guided FUS to open the BBB for chemotherapy delivery to brain tumors. The study is a prospective, single-arm, non-randomized trial that will include six patients with high-grade glioma. The ExAblate 4000 Transcranial (220 kHz) system is used in combination with Definity® ultrasound contrast to open the BBB and deliver liposomal doxorubicin. The trial involves a two-stage procedure. On the first day patients receive chemotherapy infusion followed by FUS, and confirmation with gadolinium enhancement on MRI. On day 2 the patient undergoes surgery for tumor removal. FUS was applied in a 3x3 grid, and 3 mm spacing, with 300 ms at each spot. One patient has been treated to date. The results of doxorubicin levels and histological analysis are in progress and the trial continues to enroll patients.

Hao-Li Liu from Chang Gung University Taiwan discussed the use of focused ultrasound-induced BBB opening to enhance bevacizumab delivery to the central nervous system (CNS) for malignant glioma treatment in animal models. Their preclinical model mimics the human treatment experience. Rats undergo 5 weeks of bevacizumab treatment, an anti-angiogenic agent, plus BBB opening with FUS (0.5 MHz, burst exposure, Sonovue IV administration (0.4 or 0.8 MPa)). Gadolinium enhancement was used to visualize BBB opening followed by HPLC quantification and western blot. Gadolinium enhancement demonstrated a BBB opening effect. HPLC measurements showed enhanced bevacizumab penetration into the CNS with FUS compared to non-sonicated controls. CD-31 staining showed a therapeutic effect of bevacizumab. Tumor progression was reduced, and overall survival also improved with the combined treatment.

Colleen Curley from UVA discussed a mouse model of glioma treated with non-viral miRNA-34a gene vectors delivered via FUS BBB opening. BPNs were used for delivery of miRNA-34a, oncogenic protein targets, as a glioblastoma therapeutic. FUS delivery of miRNA-34a decreased tumor size in mouse glioma. Further research will analyze miRNA and target protein levels in tumors, and evaluate proliferation and apoptosis in tumors.

Nathan McDannold of Brigham and Women's Hospital presented on closed-loop control of targeted drug delivery via focused ultrasound-induced opening of the BBB and blood-tumor barrier (BTB) in a F98 rat glioma model. The aim is to develop a real-time monitoring system for BBB opening. The team developed a closed-loop cavitation-based controller to detect BBB opening using harmonic emissions and broadband emissions to suppress the likelihood of damage. The system employs two transducers with overlapping foci to create small openings in the BBB/BTB, and allows control of a predetermined level of acoustic emissions. Results showed that they were able to modulate cavitation by controlling harmonic emissions, while keeping broadband emissions at bay, during sonication in vivo. They were also able to achieve controlled drug delivery with BBB opening. Additionally, they are working on controlled chemotherapeutic drug delivery in a rat tumor model.

Nathan McDannold also presented on antibody delivery in a brain metastasis animal model (rat) of breast cancer. The objectives of the study were to evaluate the treatment benefit of two antibody therapies that

target the HER2-receptor, using focused ultrasound-mediated BBB disruption for delivery of the antibodies to the brain. The model used was MDA-MBI-361, a cell line derived from HER2-positive cells from a breast cancer brain metastasis model. Treatment antibodies were the HER2-targeting antibodies: trastuzumab and pertuzumab. Animals received six weekly treatments. Sonication parameters included: 690 kHz, 60 s duration, 10 ms bursts, and 1 Hz burst frequency. Four to 14 sonications were used per session to treat the entire tumor. In the FUS plus antibody treatment group, only four out of ten animals responded to treatment, and no animals responded in the control and antibody-only groups. BBB disruption was successful in all groups. In conclusion, FUS BBB disruption with antibody therapy was able to slow the growth of brain metastasis from breast cancer.

Alexandre Carpientier from Sorbonne University (Paris) discussed a clinical trial of BBB disruption by pulsed ultrasound using an implantable pulsed ultrasound device (SonoCloud® device). This device opens the BBB with contact ultrasound in combination with microbubbles. The SonoCloud device is a 1 MHz, 10 mm transducer with an unfocused ultrasound emission. The device is implanted in a surgeon's burr hole during surgical resection. There is a transdermal needle connection with an external dedicated generator. Preclinical research in mice, dogs, and nonhuman primates showed efficacy. A phase I/IIa clinical trial is assessing feasibility of this device in patients with recurrent glioblastoma (2 to 30 patients), treated with carboplatin chemotherapy and five escalating ultrasound dose levels. The trial is ongoing and 15 patients have been treated to date. Forty-one ultrasound treatments have been performed in these 15 patients, and there have been 28 total BBB disruptions (in 11 patients). There is increased BBB opening with higher acoustic pressures. Although efficacy is not the goal of this early trial, one patient has had tumor control for 12 months.

Zhiyuan Xu from UVA presented on sonodynamic therapy for the treatment of C6 glioma in a rat model. Sonodynamic therapy utilizes low-intensity ultrasound in conjunction with a sonosensitizer, resulting in autophagy and apoptosis secondary to reactive oxygen species. 5-aminolevulinic acid (5-ALA) and verteporfin were assessed as treatment agents in a rat glioma model (C6). Three hours after verteporfin or 5-ALA administration via tail vein, the animals were sonicated (1.1 MHz) to maintain a tumor temperature at 42°C for 20 minutes. Combination treatment significantly increased necrosis in the tumor. Further histology results to assess apoptosis in this tissue are pending.

Jonathan Sukovich from the University of Michigan presented results from in vivo histotripsy brain treatments in a pig model. Histotripsy is a non-thermal therapy that relies on high amplitude, short-duration ultrasound pulses to generate targeted cavitation bubble clouds to mechanically fractionate tissues. It does not generate heat, and therefore can potentially treat targets closer to the skull. Objectives of this 72-hour survival study were to demonstrate safety and feasibility in pigs after craniectomy. Histotripsy was able to generate lesions of arbitrary shapes and sizes in brain tissue. Precision targeting and real-time monitoring was possible using ultrasound imaging. Histotripsy damage in the brain was detected and evaluated by MRI. There was minor edema observed surrounding one lesion at 72 hours after treatment, yet no evidence of hemorrhage beyond the boundaries of gyrus-confined lesions. Overall, histotripsy treatments in the brain were well tolerated, no animals died during treatment and no problems were reported during the 72-hour recovery time. Pathological findings showed no evidence of hemorrhage or encephalitis beyond the lesion area and there was no evidence of inflammatory infiltrate. Within the lesion, there was evidence of hemorrhage and tissue disruption with significant macrophage influx. Overall, the changes resembled that of a confined, sub-acute infarct.

Shih-Ying Wu from Columbia University presented on neuronavigation-guided FUS-induced BBB opening in nonhuman primates, utilizing real-time acoustic mapping evaluation. Wu described the development of a device that uses imported images (acquired beforehand) with a neuronavigation system to enable accurate targeting of a FUS device. The mobile system demonstrated accurate guidance for both sonication and cavitation mapping, a fast procedure time (30 minutes) and flexible targeting. The system is translatable to the clinic, but requires validation.

Immunotherapy

Presentations highlighted the use of FUS, alone or in combination with immunotherapeutics, to enhance the anti-tumor immune response.

Gail ter Haar from The Institute of Cancer Research presented initial results of in vitro experiments investigating whether thermal exposures using a polymerase chain reaction thermal cycler can induce immunogenic cell death. Previous research showed that thermal insult can induce cell death and the activation of heat shock response in cancer cells. Thermal exposures increased calreticulin levels and decreased CD47 expression on the cell surface (HCT116; human colon adenocarcinoma). Pilot data suggests that thermal exposure may increase ATP secretion from HCT116 cells. Thermal exposure of cancer cells in vitro induced markers of immunogenic cell death. This data suggests that thermal exposure induces cells to become more immunogenic. The next steps will be to investigate whether FUS-induced thermal exposures can enhance the anti-tumor efficacy of immune checkpoint inhibitors in vivo in a pancreatic cancer cell model.

Kelsie Timbie from UVA discussed melanoma growth control via ultrasound and the role of the adaptive immune system. The objectives of the study were to investigate whether FUS in combination with microbubbles can enhance the baseline T cell responses of tumors in vivo (B16F10 subcutaneous tumor in a C57B16 immunocompetent mouse model). Mice were treated with a PD-1 inhibitor and FUS with microbubbles. Ultrasound alone significantly improved tumor control and overall survival compared to treatment with a PD-1 inhibitor alone or ultrasound and PD-1 inhibitor combined. Both FUS and PD-1 inhibitor treatment promotes an anti-tumor immune response (increased CD4, CD8, and regulatory T cells). Next, they tested whether FUS alone was activating the innate immune system in a Rag1 knockout mouse (immunocompromised) and found no effect of FUS on tumor growth control. This suggests that FUS interacts with the adaptive immune system. The group tested for some possible mechanisms by using adoptive cell transfer in combination with FTY720 (prevents immune cell trafficking). FUS increases immune cell trafficking, but not proliferation. Future studies will investigate whether ultrasound increases immune cell activation.

Karin Skalina from the Albert Einstein College of Medicine presented results on the stress response of cancer cells after low-intensity FUS as an immune priming agent. Low-intensity FUS (Philips Therapy and Imaging Probe System (TIPS)) with minimal focal intensity (300-600 W/cm2), 1.0 MHz frequency, 3 to 5 W of power, 100% duty cycle, at 1.5 second duration was used. In vitro experiments demonstrated that low-intensity FUS increased cell surface calreticulin and intracellular HSP70. In three different cancer cell lines (pancreatic, prostate, and lymphoma) surface localization of molecular chaperones (HSP70, calreticulin, and Grp78) were enhanced 6 hours after treatment. Low-intensity FUS did not result in cell death. Treatment increased tumor cell phagocytosis and dendritic cell activation. The group also performed in vivo treatment using low-intensity FUS in combination with ablative radiation in a B16-M1 mouse melanoma model. Results showed long-lasting primary tumor growth control with a T cell mediated reduction in metastases.

Matthew Silvestrini from the University of California at Davis discussed FUS-activated nanoparticle delivery in a mouse breast cancer model. The experiment administered copper doxorubicin liposomes intravenously, sonicated the tumor, and administered CpG oligodeoxynucleotide (CpG) intratumorally in a mouse model of breast cancer. The combination treatment induced a local inflammatory response and reduced systemic tumor growth. Adding a PD-1 inhibitor to the treatment was very toxic, resulting in death of 50% of the animals. A priming protocol was developed to administer PD-1 inhibitor with CpG first, followed by chemotherapy. This resulted in a complete systemic response in 50% of treated animals. Future studies will look at CD8+ T cells, and functional inflammatory and anergy assays.

Franco Orsi from The European Institute of Oncology (Milan) discussed the abscopal effect after FUS treatment of advanced pancreatic cancer. The abscopal effect refers to the action of local therapy upon distant tumors. Patients with pancreatic cancer were treated with thermal ablation (N=72). The goal of the treatment was pain relief. FUS was safe and feasible for treating pancreatic cancer for both debulking and palliative purposes. In 4 patients, an abscopal effect was observed. More data about the immunological responses will be collected in a dedicated registry to understand this effect.

George Schade from the University of Washington discussed the immune response to boiling histotripsy ablation of renal carcinoma in the Eker rat model. Boiling histotripsy produces non-thermal mechanical tissue destruction. The Eker rat model is a naturally occurring syndromic model of renal cell carcinoma. Tumor targeting was successful in all treated rats. There were short-term immune changes including altered cytokines and increased tumor CD8+ T cells and M1 macrophages. A long-term study is in progress and will help to fully characterize the immune response.

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Panel Discussion: Immunotherapy

Panel Moderators: T. Bullock. Panelists: K. Ferrara, C. Guha, F. Orsi, G. Shade, and G. ter Haar.

The panel discussed their opinions on the following topics:

1. **For histotripsy, does the entire tumor need to be ablated, or does partial ablation work to stimulate the immune response?**
   Partial ablation is being done in the histotripsy experiments due to limitations with image-guidance and to ensure a good margin for safety and reduce the risk of bleeding or other complications. The panel also mentioned that if histotripsy is indeed stimulating the immune response, partial ablation should achieve this effect without having to ablate the entire tumor.

2. **A follow-up question for Dr. Orsi was asked regarding whether the treatment methods were thermal or mechanical and whether there were concerns regarding cavitation and safety.**
   Orsi responded that the ablation was mechanical due to the rapid feedback from the FUS system, thermal ablation usually takes several minutes. A safety margin is maintained between the target region and other nearby organs. As part of the procedure, the skin is compressed and this reduced the blood flow into the FUS-treated area and the only area affected by FUS is the targeted region.

3. **After histotripsy, TNF-α and HMBG1 are elevated indicating stimulation of an immune response. IL-10 is also elevated, which is more of an anti-inflammatory immune response; could this be the repair mechanism of the kidney? Are there two responses stimulated by histotripsy**
   Yes, it seems likely that there is an early inflammatory response followed by repair mechanisms.

4. **The panel was asked to share their opinions on any possible concerns with translation of these modalities to the clinic.**
   There is some concern that combining immunotherapies or chemotherapy with immunotherapy could lead to toxicity in some patients. Another concern is maintaining the monitoring capability of thermal and mechanical effects with MRI-guidance, it would also be important to use real-time monitoring to monitor effects on T cell populations. Another issue is determining histotripsy parameters in human patients and the appropriate timing for combining with immunotherapy.

5. **Are there any differences in systemic responses to different FUS protocols?**
   This needs to be studied in preclinical models. Ablation seems to be a humoral response only, but priming with FUS might help induce a T cell response. More modeling is needed to understand the best biomarkers to use for studying the immune response. There are two mechanisms at play in the immune response to FUS: physical and biological mechanisms. There was a suggestion that there is a need to monitor physical parameters such as temperature and cavitation. It is also difficult to compare across studies at this time, as every group has a different model, and a different FUS protocol. Ultimately, direct comparisons will be necessary to move the field forward.

6. **What do we need to know going forward?**
   The panel agreed that there is a need to characterize the adaptive immune response, as only immune priming has been studied so far.

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Liver/Pancreas – Technical

Presentations on the technical aspects of FUS for the treatment of liver and pancreatic cancers ranged from choice of mechanism (thermal ablation or histotripsy) to overcoming technical challenges such as correcting for breath motion.

Vera Khokhlova from the University of Washington presented on the use of shock-wave exposures for accelerating thermal ablation of localized tissue volumes. There are several clinical challenges for the use of thermal ablation that may be mitigated by nonlinear shock-wave heating. Khokhlova investigated whether shock-wave heating via boiling histotripsy is possible with a clinical-FUS system (Sonalleve V1) in bovine liver samples. Results demonstrated that volumetric thermal lesions could be generated utilizing shock-wave exposures with a clinical-FUS system. Trajectories were optimized to enable more uniform shock-wave heating. Shock-wave exposures can accelerate thermal FUS to reduce heating of near-field and surrounding tissues, mitigate diffusion and perfusion effects, and provide sharper treatment margins.

Zhen Xu from the University of Michigan presented results on rapid ablation of large tissue volume using histotripsy with electronic focal steering This process can be made more efficient by strategically ordering the temporal and spatial position of foci within the steering sequence by minimizing cavitation memory effect. This preliminary research is ultimately aimed at the treatment of liver cancer in human patients. Experiments were conducted in red blood cell phantoms. Different steering sequences were investigated: raster, random, and structured. The group achieved an ablation rate of 2-4 mL/minute and also confirmed their results in bovine liver and demonstrated that structured scanning was the best option to achieve ablation.

Sabrina Haase from Fraunhofer spoke on the TRANS-FUSIMO system, a prototype for focused ultrasound treatment of the liver under breathing motion. The TRANS-FUSIMO system uses an MRI scanner and a focused ultrasound device in coordination with treatment software. Prior to treatment an offline atlas for ultrasound is made by observing motion with 4D-MRI for motion prediction. During therapy, real-time motion tracking and temperature monitoring are completed using MRI. The system is still in development for use in an in vivo pig study for validation testing. Animal trials will begin soon, and could lead to human clinical trials at the end of 2017.

Arianna Menciassi from the Biorobotics Institute discussed a multifunctional robotic platform for ultrasound-guided FUS. The FUTURA project is to design a platform for FUS treatment with robotic arms for accurate positioning, and combine this with advanced tracking through ultrasound imaging data. FUTURA focuses on multimodal reconstruction aspects, sensors for fusion algorithms and safety strategies, and machine learning implementation. Models have been developed and tested in in vitro phantoms and ex vivo tissues to assess targeting, sonication, and lesion monitoring. Pretreatment, the system performs 3D ultrasound scanning, organ registration (image fusion), and therapy pre-planning. The ultimate goals for this system are to increase the number of clinical applications, shorten the duration of procedures, increase safety, reduce costs, and promote the widespread diffusion of FUS into routine clinical practice. The target organ for the system is the kidney.

Jan Strehlow from Fraunhofer spoke on real-time MR imaging and ultrasound motion tracking for abdominal FUS. The objective of their work is to develop reliable motion tracking of abdominal organs like the liver and kidney to improve FUS treatment. To meet these goals, they have developed a MR-compatible ultrafast ultrasound beamformer system for motion tracking. A tracking algorithm based on conditional density propagation has been developed. Using the particle filter approach there is automated landmark detection, linear transformations (translation, rotation, and scaling), and a two-level approach for global and local estimation. Preliminary evaluation demonstrated that the system is feasible, reliable, and offers sufficient precision for real-time motion compensated HIFU therapy. Next, the team will test this in a clinical study set to begin in 2017.

Thomas Payen from Columbia University discussed pancreatic tumor monitoring and treatment using harmonic motion imaging for FUS in a transgenic mouse model. Harmonic motion imaging uses the mechanical properties of the target tissue by estimating displacements induced by periodic acoustic radiation force. This technique allows simultaneous tissue ablation and monitoring without interruption of FUS and focal spot localization. The harmonic motion imaging system was tested in a mouse model of pancreatic cancer. Experimental results demonstrated that harmonic motion imaging could generate in vivo displacement maps for pancreatic cancer, monitor FUS effects on mechanical properties during sonication and detect lesion formation. The next steps will be to perform a longitudinal study for long-term effects of FUS on tumor mechanical properties, and to perform experiments in resected human pancreatic tumor.

Matthew Adams from Stanford University discussed preliminary work integrating deployable reflectors and fluid lenses with endoluminal ultrasound to enhance and dynamically adjust focal gain and depth. He described the design of an endoluminal/intracavity HIFU device that can be used to create localized, and spatially precise, thermal ablation in tissue targets adjacent to body lumens. The device will have a deployable applicator design that is compact during device delivery and can be deployed at the target site, which can be enhanced to the desired therapeutic size. The device will consist of a tubular transducer with an acoustic reflector balloon, an adjustable fluid lens balloon, and a larger effective aperture at the bottom. Acoustic and thermal modeling showed efficacy of the device. A modular assembly was created to measure the focal patterns at different length distensions. Preliminary theoretical and experimental analysis illustrated enhanced acoustic output, focal gain, and treatment depth versatility.

Liver/Pancreas – Clinical

Presentations on the use of FUS in preclinical and clinical studies for the treatment of liver and pancreatic cancer highlighted techniques to treat structures within the abdomen.

Joan Vidal-Jove from the Hospital University Mutua Terassa presented early clinical results using concurrent low dose fractionated ultrasound with chemotherapy in abdominal tumors. Vidal-Jove described two cases of the use of pulsed hyperthermia FUS combined with FOLFOX or panopazib. They hypothesize that pulsed hyperthermia with FUS may increase tumor permeability to chemotherapy. No toxicities or complications have been observed. Clinical results are encouraging, but there is not yet enough data to evaluate significance. In summary, FUS with pulsed hyperthermia is a feasible technique with low morbidity and encouraging results in patients with advanced abdominal tumors.

David Melodelima from INSERM discussed the clinical experience with intraoperative HIFU in patients with colorectal liver metastases. Tumor ablation is viewed as a complementary tool in patients that are not suitable for resection. A toroidal transducer was created to increase the focal zone in depth. The ablation rate is 10.5 mL/min. In vivo studies showed efficacy, so clinical studies were carried out. The clinical studies aimed to assess the feasibility and safety of HIFU ablation in patients undergoing hepatectomy for colorectal liver metastases, as well as to collect preliminary efficacy and accuracy data. The phase I/IIa study (N=28) demonstrated that the demarcation between ablated and non-ablated tissue was clearly apparent in ultrasound images and histology. A phase IIb (N=11) study is underway. In conclusion, the toroidal HIFU transducer achieved fast, selective, safe, and well-tolerated large volume liver ablation.

Samantha Tucci from the University of California at Davis discussed [18F]-FDG PET and contrast MRI for enhanced guidance of FUS ablation in a syngeneic orthotopic model of murine pancreatic adenocarcinoma. They used a Bruker BioSpec 7T Image Guided Therapy System for single point ablations or circle ablations of a larger volume. The current tumor model parameters led to rapid disease progression and aggressive local invasion, so a less aggressive cell line will be used in future

experiments. Future studies plan to look at the delivery of nanotherapeutics including squalene-gemcitabine, paclitaxel, and immunotherapeutics.

Matthew Adams from Stanford University presented on endoluminal ultrasound applicators for thermal ablation of pancreatic cancer under MR-guidance. The endoluminal transducer performs sonication through the gastrointestinal wall into the tumor. The group created three different transducer shapes: 3.2 MHz planar, 3.3 MHz curvilinear (lightly focused), and 3.2 MHz curvilinear (strongly focused). In vivo pig studies were performed to evaluate the three transducer shapes. Real-time MRI and gross evaluation of treated tissues demonstrated the capability of targeting and ablating pancreas tissue through the stomach wall. The next steps will be to develop endoscopic steering control for positioning/delivery.

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Prostate

Prostate tissue ablation with FUS was FDA approved in 2015. Presentations focused on the history of developing this treatment for the clinic, methods to improve current techniques, and expanded indications for FUS for the treatment of prostate cancer.

Christian Chaussy from the University of Regensburg reviewed the history of thermal ablation with HIFU in primary localized prostate cancer. Preclinical work began in 1989 and the first European multicenter clinical study began in 1995. Over the years the technology has developed from a prototype into the Ablatherm system, a commercial device with integrated imaging. Fourteen years of follow-up with data from Munich suggest a high rate of cancer-specific survival and freedom from salvage therapy requirements in patients with low risk disease. HIFU is highly attractive as a minimally invasive treatment for prostate cancer either as a primary or salvage therapy. It is also feasible for focal treatment of prostate cancer with promising oncological results and limited morbidity. The technological development of devices with new ultrasound technologies or MRI guidance will increase the role of this therapy in the near future.

Christian Chaussy also presented on local radical tumor ablation through combined transurethral resection and transrectal HIFU in patients with high-risk prostate cancer. Chaussy described results from a long-term cohort study of radical local ablation of high-risk prostate cancer (N=480). Results demonstrated that cancer-specific survival at 10 years was 92.9%. Chaussy mentioned that they hypothesize that HIFU also modulates immune response.

Stephen Scionti from Virturo Heath spoke on the early experience with HIFU in the US. The FDA approved HIFU for the Sonablate device on September 9, 2015, but stipulated that training must be provided. The Ablatherm Integrated Imaging system was granted 510k approval by the FDA for prostate tissue ablation on November 6, 2015. Virturo Health was formed in October 2015 to deploy HIFU in the US and a physician training program has been developed. They have also developed a MRI-Fusion guided FUS workflow. To date, 114 patients have been treated by Virturo Health. Early results show good PSA response with a low incidence of side effects. The 3-month continence rate is 99.1% and the endoscopic surgery intervention rate is 1.7%. Pre-FUS TURP in whole-gland treatments avoids the use of SP tube with average Foley catheter time of 6.9 days. MRI-Fusion biopsy and MRI-Fusion guided FUS allows a personalized approach based on tumor burden and location while minimizing side effects.

Rajiv Chopra from UT Southwestern Medical Center discussed MRI-guided transurethral ultrasound ablation (TULSA) of localized prostate cancer. MRI-guided TULSA is minimally invasive with real-time temperature feedback, and the procedure takes less than 45 minutes to treat the entire gland. A phase I clinical trial (N=30) was published this year (Chin et al. Eur Urol, 2016). After 24-months of follow-up, there was a PSA reduction, no rectal injury or fistula, or Grade 4 adverse events. Clinical histology showed an 88% reduction in median prostate volume. The results of this first trial suggest that TULSA is clinically feasible with low toxicity and a good safety profile. This group of patients will be followed for 5

years. Next, a larger study is underway (N=100) with the following endpoints: ablation efficacy, safety, and biopsy. The target temperature will also be increased in this trial for complete whole-gland ablation.

Lili Chen from Fox Chase Cancer Center talked about the therapeutic effects of pulsed HIFU combined with encapsulated chemotherapeutic agents for prostate cancer in a mouse model (LNCaP). The chemotherapeutic agents were encapsulated in the hydrophobic shell of perfluorocarbon droplets. In this study the encapsulated agents were paclitaxel and docetaxel (20 mg/kg). Mice were treated with pulsed HIFU (ExAblate 2000): 1 MHz, 25W acoustic power, 10% duty cycle, and each sonication lasted 60 seconds. Tumor volume was measured weekly on MR imaging for 4 weeks after treatment. Results showed a significant reduction in tumor volume with the combination of HIFU and paclitaxel or docetaxel. In conclusion, these studies demonstrated potential for the combination of prostate cancer therapy with nanodroplets activated by pulsed HIFU.

Kenneth Bader from the University of Cincinnati spoke on the use of passive cavitation imaging for monitoring histotripsy ablation. For clinical treatment of benign prostate hyperplasia with histotripsy, mechanical ablation with shock-induced microbubble clouds is used. Hyperechogenecity and cavitation emissions are being tested as methods to monitor treatment progress. Prostate phantoms were used to test these monitoring systems. Both hyperechogenecity (B-mode imaging) and cavitation emissions could detect the bubble cloud. Passive cavitation emissions were a better predictor of mechanical ablation characteristics and were significantly better for sensitivity. Both imaging modalities significantly predicted the ablation zone. In conclusion, accuracy and sensitivity were significantly better for passive cavitation imaging as compared to B-mode imaging.

Narenda Sanghvi of SonaCare Medical discussed monitoring tissue change during HIFU treatment of prostate cancer using the Sonablate system. The goal of their study was to quantify tissue changes based on backscattered RF signal data during HIFU treatment. The attenuation coefficient and backscatter signal amplitude increased with temperature as the tissue became necrotic. Next, these findings were validated with real-time thermometry during HIFU treatment in five patients with prostate cancer. In summary, RF-backscattered signals provide necessary quantitative feedback for improved efficacy for the treatment of prostate cancer with HIFU.

Christian Chaussy discussed focal therapy with HIFU in low-risk prostate cancer. Focal therapy does not aim to ablate the whole gland, but only treat areas of known cancer lesions in the prostate gland. He described preliminary results from a small trial in 66 patients. PSA was reduced after HIFU treatment and there were no significant therapy-related side effects during the follow-up period. Small trials for focal therapy have also been conducted in the UK and France. Results from these studies suggest that focal HIFU produces freedom from clinically significant prostate cancer with a low rate of genitourinary side effects. Focal salvage therapy is a potential strategy for localized recurrence after radiotherapy that may reduce the harm resulting from whole-gland salvage therapies.

Arjun Sivaraman from the Institut Montsouris described an initial clinical experience with HIFU hemiablation versus MRI-guided 'lesion only' ablation of prostate cancer. This presentation focused on genitourinary functional outcomes and complications (N=85). Genitourinary functional outcomes were evaluated pre- and post-operatively. HIFU lesion only ablation demonstrated lower incontinence rates and better erectile function preservation compared with hemiablation. Oncological outcomes from this study are in process.

Arjun Sivaraman also discussed the treatment experience with the MRI-ultrasound fusion guided HIFU using the Focal-One® system. Eighty-five patients were treated for localized prostate cancer. Fifteen percent of all cases had complications (Clavien grade II). Mean hospital stay was 1.8 days, and the bladder catheter was removed on day 2. For the first 40 cases, mean PSA reduction was 53%, but nine patients had higher PSA post-treatment. All patients were continent at 3 months and potency was maintained in 83% of preoperatively potent patients. MRI-ultrasound fusion guided HIFU treatment appears to be safe with low rates of complications.

Jim Hu from Weill Cornell Medicine spoke on the current state of HIFU for prostate cancer in the clinic. Ultrasound delivery to the prostate is noninvasive and may be repeated. HIFU 12-month partial gland ablation outcomes report that 54% of patients are continent, potent, and cancer-free. As the treatment guidelines have changed, fewer men are undergoing treatment for low risk disease. Next, Hu spoke about the value of a device registry for stakeholders. For patients a registry could help estimate out of pocket costs ($25,000), advise on short and long-term outcomes, side effects, and comparative effectiveness versus traditional therapies. For device manufacturers, a registry would acquire data enabling a specific prostate cancer indication from FDA, allow for wider adoption with Center for Medicare and Medicaid Services (CMS) and approval from payers, and attain feedback in terms of quality and outcomes for research and development. For health plans, the registry would provide comparative effectiveness, help aggregate costs over time, and estimate costs of treating potential complications. For physicians, a registry would provide data to counsel patients, optimize patient selection, develop post-treatment surveillance protocols, and refine techniques to rapidly overcome learning curves. A framework for a registry was proposed with the following critical outcomes: tumor characteristics, extent of HIFU treatment (focal vs. whole gland), longitudinal patient reported outcomes, safety and complications (Clavien grade), cancer control outcomes (PSA, MRI, and biopsy), and comparison to competing therapies.

Bone Tumors

Presentations discussed the use of FUS for treatment of osteoid osteoma and painful bone metastases.

Qingguo Wang from Shanghai First Republic Hospital presented on factors affecting the efficacy of MRI-guided FUS ablation for painful bone metastases in a multicenter clinical study in China. Pain from bone metastases contributes substantially to morbidity and mortality in patients with malignant carcinoma. MR-guided FUS destroys the nerve endings on the periosteum of diseased bone. The MRI-guided system allows the physician to identify and target tumors, and provides real-time thermometry of the treated tissue. A preliminary study was conducted for the treatment of pain in patients (N=70) with bone metastases. BPI-quality of life scores were significantly increased after treatment. Results demonstrate that MR-guided FUS is a safe and effective method for treating painful bone metastases. Patients with osteogenic metastases and solitary metastases had better efficacy, suggesting future studies for MRI-guided FUS in this patient population.

Alberto Bazzocchi from Rome Sapienza University spoke about local control of bone metastases with MRI-guided FUS. The primary endpoint of their study was the number of lesions with partial or complete responses at 3 months. Fifty-one patients (56 lesions) were treated, 22% of patients had a complete response and 28% had a partial response. Results suggest that lesions with the following criteria make good candidates for ablation with the intent to control the lesion: completely accessible margins, small (<7 cm) and with no or limited soft-tissue involvement, or osteolytic pattern.

Robert Staruch from UT Southwestern Medical Center presented on MR-guided HIFU hyperthermia-mediated drug delivery using thermosensitive liposomes (ThermoDox) in an animal model (rabbit Vx2 tumors). The aim of this research is to improve local control of hyperthermia-mediated doxorubicin delivery without increasing systemic toxicity. Thermosensitive liposomal doxorubicin releases in the tumor without affecting doxorubicin levels in the heart (systemic toxicity). The study investigated whether heating the tumor for a longer period of time would increase the therapeutic efficacy of doxorubicin in a rabbit model. Results showed that prolonged heating (40 minutes) increased tumor doxorubicin levels and increased the therapeutic ratio. Doxorubicin levels in the heart remained unchanged during prolonged heating.

Pejman Ghanouni of Stanford University discussed the parameters that predict successful MR-guided FUS treatment of painful osseous metastases. Previous research demonstrated that the true response rate for MR-guided FUS treatment of osseous metastases was underestimated because of patients that were sub-optimally treated. Images from previous treatments were analyzed (N=112). An imaging feature called the 'black band' was identified that correlated with response to treatment. The energy density on the bone surface (EDBS) was correlated with both the black band and pain relief. In technically successful treatments (black band positive, and EDBS>5), the clinical response rate was 86%. The black band is a sensitive post-treatment imaging finding that predicts successful treatment. Higher EDBS is a specific technical parameter that increases the likelihood of pain relief after treatment. The research group suggests that EDBS should be tracked during treatment.

Pavel Yarmolenko of Children's National Medical Center presented technical aspects of feasibility, safety, and initial efficacy of osteoid osteoma ablation with MR-guided HIFU. Current treatments are limited (surgery or radiofrequency ablation). A preliminary investigation of MR-HIFU was carried out in nine patients. To optimize osteoid osteoma treatment, pretreatment patient positioning was important. Power increased and sonication number decreased with experience, and sufficient energy/thermal dose was achievable with as few as three high-power sonications. Greater operator control of sonication duration may allow shorter treatments. Small lesion size requires focused heating and high-resolution imaging for planning. Both deep and shallow lesions in bone were treatable. In some cases, with deep lesions and/or thick cortex, effective treatment may require some adjacent soft-tissue damage due to limitations with the current equipment. This might be improved by the availability of lower HIFU frequencies. Optimizing imaging coils may allow better intraprocedural imaging and tracking of thermal dose in 3D.

Alex Chisholm from the University of Toronto spoke on simulating heat transfer in bone during MRI-guided FUS. A pilot trial was carried out in five patients with osteoid osteosarcoma, and demonstrated no pain in four patients after treatment, and significantly less pain in one patient after 2 treatments. Next, the team wanted to develop a GPU-based MRI-guided HIFU simulator for clinical treatment planning/assessment with the goal of being able to reproduce heating distributions for clinical HIFU treatment of bone tumors. The K-Means algorithm was used for automatic segmentation of an unlabeled MR image to differentiate bone from muscle. Acoustic simulations were carried out. They were able to reproduce temperature distribution with a computer simulator. This will enable pretreatment planning and intraoperative assistance, and predict treatment temperature in bone.

Maayan Kimhy from Sapienza Universita di Roma discussed MRI-guided HIFU for noninvasive treatment of osteoid osteoma. The purpose of this study was to determine the feasibility and clinical efficacy of MRI-guided FUS for pain relief. This was a prospective study with 29 patients. Primary endpoints were adverse events and pain relief. A complete clinical response was found in 93% of patients in terms of absence from pain and no intake of NSAIDs. Pain recurred in one patient, 3 months after treatment. Two patients (0.6%) reported pain recurrence requiring radiofrequency ablation. Treatment was well-tolerated and no adverse events were recorded. Imaging with CE-MRI demonstrated edema and hyperemia decrease in every lesion associated with a complete response. In conclusion, MRI-guided HIFU for osteoid osteoma is effective and noninvasive with no adverse events.

Alessandro Napoli from Sapienza Universita di Roma presented on MR-guided FUS for the treatment of osteoid osteosarcoma in a prospective study. Feasibility of treatment was a concern; if the target is too deep, FUS will not work. Preliminary treatment was performed in 45 patients. Results so far suggest a complete absence of adverse events, durable clinical efficacy, and a good tolerance profile.

Michael Temple from the Hospital for Sick Children, Toronto presented preliminary results from MRI-guided HIFU of osteoid osteoma in pediatric patients. A pilot study of ten patients was conducted to assess pain, quality of life, and use of pain medications, as well as compare treatment thermometry with patient-specific simulations. Six patients have been treated to date; treated bones include femur, fibula, and calcaneus. Results showed 86% technical success, 80% of patients had complete responses (4/5), and

20% had partial responses. There were no serious adverse events. Pain scores were also reduced by treatment. In summary, HIFU was an effective method of treatment that reduced pain and improved quality of life. Patient selection is important, and treatment parameters need to be optimized for future studies.

Karun Sharma from Children's National Medical Center discussed noninvasive treatment of painful osteoid osteoma in children. He described a prospective trial of 12 patients for safety and feasibility. Nine patients have been treated to date. Treatment was feasible in all patients with no adverse events. Complete responses were seen in 89% of patients, and 11% of patients had a partial response. Responses were durable up to 12 months. Treatment, anesthesia, and recovery time were similar to radiofrequency ablation.

Wednesday
August 31, 2016

Breast Tumors

Presentations highlighted clinical trials and preclinical studies assessing FUS for the treatment of breast cancer and breast fibroadenoma.

Carrie Rochman from UVA discussed preliminary findings from a clinical trial of ultrasound-guided FUS ablation for the treatment of breast fibroadenomas (benign breast tumors). Current management includes observation or surgical excision. The trial enrolled 20 patients to evaluate feasibility, tumor response, patient experience, and safety. The device used for treatment is the Echopulse™ and uses alternating ablation and cooling cycles, with pulse power adjusted to create visible denaturing of the tissue. During treatment, ultrasound imaging shows a hyperechoic region produced at the focal zone. Boiling of the tissue can occasionally be seen, and edema may develop within the surrounding breast tissue. All twenty patients have been treated, and 10 remain in follow-up. There have been no grade 3 adverse reactions to date. The researchers conclude that the procedure is well tolerated by patients, has minimal toxicity, and appears to be effective.

Roussanka Kovatcheva from University Hospital of Endocrinology presented findings on the long-term efficacy and tolerability of ultrasound-guided HIFU treatments for breast fibroadenoma. Twenty patients were treated with HIFU (Echopulse), and ultrasound examination and volume were performed at baseline, 6, 12, and 24 months after treatment. Some patients were treated only once, while others were treated twice. There was a significant volume reduction at 2 years of follow-up. This study demonstrated that ultrasound-guided HIFU ablation is a safe and effective treatment for breast fibroadenoma with excellent long-term efficacy. Patients that received repeated treatment showed better results. Fibroadenoma shrinkage continued for 3 years after treatment.

Michael Douek from King's College London spoke about a clinical trial of HIFU treatment for breast adenocarcinoma. This trial examined whether circumferential HIFU treatment (N=20) could isolate the tumor from its blood supply and reduce treatment time. Outcome measures were a reduction in symptoms, reduction in treatment time, feasibility to achieve a 50% reduction in volume after 6 months, and a decrease in volume compared to the control group. Results suggest that circumferential HIFU is feasible. There was a significant reduction in volume compared to control patients.

Yang Han from Columbia University presented on harmonic motion imaging for characterization and monitoring of FUS for ablation of post-surgical breast tumors. Harmonic motion imaging for FUS utilizes an amplitude-modulated HIFU beam for both tissue displacement measurements and thermal ablation. The goal of the study was to develop, optimize, and test a harmonic imaging system for breast tumor characterization and ablation monitoring. Breast tumor pathology samples were used for testing. Experiments demonstrated that harmonic motion imaging was capable of mapping and differentiating normal and pathological breast tissues in post-surgical breast specimens. Future work will focus on real-time monitoring and in vivo testing.

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Other Tumors

Presentations highlighted the use of FUS for a variety of tumors including desmoid, pediatric sarcoma, lung, and thyroid.

Matthew Bucknor from the University of California at San Francisco discussed the early clinical experience with MRI-guided FUS for treatment of desmoid tumors within the thigh. Desmoid tumors are benign but locally aggressive tumors that derive from fibroblasts. Conventional treatments include surgery, radiation, and chemotherapy. The recurrence rate is as high as 40%. Desmoid tumors in the thigh can have a large volume and may encase/displace the sciatic nerve. Two cases were described. Both patients

had reduced tumor volume following FUS treatment. MRI-guided FUS is quickly becoming a first-line therapy for desmoid tumors. Clinical experience has found that large volume treatments near critical structures are challenging, but feasible.

Jenny Shim from UT Southwestern presented on the anatomical distribution of pediatric sarcoma and neuroblastoma targetability with MRI-guided HIFU. A retrospective study was conducted to guide the design of initial clinical trials. Tumors were classified based on the location and surrounding structures within the ultrasound beam path. Findings suggest that most sarcoma tumors located in the extremities and pelvis are targetable. Only a small percentage of metastatic and relapsed sarcoma tumors were targetable due to their nature to arise in the lung. Neuroblastoma was less commonly targetable due to frequent intra-abdominal locations and proximity to the spine. In summary, pediatric solid tumors are anatomically targetable with MRI-guided HIFU, but further studies are needed to overcome the obstacles in targeting a lesion in the clinical setting, including depth to reach target, volume, and respiratory motion.

Frank Wolfram of SRH Wald-Klinikum Gera discussed aspects of MRI-guidance of FUS in a flooded lung model. Lung flooding is a recently developed method for lung sonography. The objectives of the study were to assess the feasibility of single lung flooding in combination with FUS for ablation of lung cancer. Resected human lung lobes and a porcine model were used for the experiments. Results demonstrated that lung flooding in the entire lung was feasible and safe. MRI images of the ventilated lung could detect high proton density, high signal contrast in tumor, and no field inhomogeneity. Future steps will aim to optimize the MRI sequence for resolution and acquisition time.

Brian Lang from the University of Hong Kong described a prospective study on the efficacy of single-session HIFU treatment in patients with benign symptomatic thyroid nodule. Surgery is the gold standard for thyroid nodules, but some patients do not want surgery and there are few alternatives at this time. To date, HIFU treatment has been effective in this patient population. The goals of the present study were to evaluate short-term efficacy (6 months), including changes in symptom severity and health-related quality of life after HIFU treatment (N=22). Patients that underwent a single session of HIFU ablation as treatment for their symptomatic benign thyroid nodule not only had significant (>60%) nodule volume reduction, but also had improved symptom score and health-related quality of life over 6 months. Ultrasound-guided HIFU ablation might be a therapeutic alternative to active surveillance for patients that do not wish to undergo surgical resection.

Roussanka Kovatcheva from the University Hospital of Endocrinology compared different treatment regimens with ultrasound-guided HIFU on thyroid nodule volume. The purpose of this study was to compare the long-term efficacy and safety of single-session and repeated HIFU treatment of benign solid thyroid nodules. Twelve patients were treated, and 8 had repeated HIFU after 3 months due to the inefficiency of the first treatment. Patients will be followed for up to 1 year post-treatment. The results after 1 or 2 HIFU treatments are similar and were tolerable with few side effects. Additionally, a second HIFU treatment is safe and effective.

Drug Delivery for Cancer

Presentations highlighted the use of FUS for the precise delivery of therapeutic agents for cancer via thermally-sensitive nanoparticles and liposomes.

Brett Fite from the University of California at Davis spoke on the combined use of FUS ablation and liposomal doxorubicin as a treatment strategy as well as the accumulation of loadedcopper-64 labeled liposomes in mammary carcinoma models after ablation. The objectives were to combine MR-guided

FUS with both long-circulating and temperature sensitive liposomal doxorubicin and track the kinetics of these liposomes. Ablation increases accumulation of liposomes within the treated tumor. Accumulation was greatest within the rim of the viable tumor. Ablation combined with liposomal doxorubicin can result in complete tumor regression even when the entire tumor cannot be ablated.

Andreas Melzer of the Institute for Medical Science and Technology presented on FUS-enhanced targeted drug delivery via cyclodextrin-based nanocarriers. A nanocarrier was designed to encapsulate liposomal doxorubicin. Cyclodextrins are sugar based cyclic molecules consisting of multiple D-glucose units linked by α–(1,4)-glucosidic bonds. Doxorubicin was successfully encapsulated within a novel γ-cyclodextran. The novel carrier is thermally sensitive and mechanically stable. In vitro experiments were carried out in high-throughput FUS systems and demonstrated increased encapsulated drug uptake in vitro (HCT 116 cells). In vivo experiments, in a small animal model, showed that MR-guided FUS could activate release of encapsulated drug at the targeted anatomical site.

Maya Thanou from King's College London discussed image-guided FUS-enhanced delivery of anticancer drugs. Thermally sensitive near-infrared-labelled (NIR) nanoparticles containing topotecan were developed. FUS heating (hyperthermia) of the tumor induces drug release from thermosensitive liposomes. The addition of MR or NIR probes coupled with lipids added dual imaging modality properties to the liposomes for image guidance. This enabled the researchers to use optical imaging to monitor tumor accumulation in vivo. NIR fluorescence imaging was also used for guidance of focused ultrasound-mediated local drug delivery of doxorubicin. Hyperthermia induced drug release from thermosensitive theranostic liposomes. Focused ultrasound-induced short-term hyperthermia, improved nanoparticle distribution in tumors, and stimulated local drug release.

Esther Kneepkens of the Eindhoven University of Technology presented monitoring of drug release from temperature-sensitive liposomes by interleaved scanning with MRI. FUS was used to heat the tumor in an in vivo model. The pharmacokinetics of doxorubicin uptake and gadolinium are different, and gadolinium clears much faster. Therefore, using gadolinium as an imaging agent may not give a true picture of doxorubicin uptake by the tumor over time. Interleaved scanning allows switching sequences dynamically to create relaxation maps and thermometry. Results of in vivo experiments showed that relaxation maps could be successfully interleaved with thermometry scans. Relaxation maps showed the release of gadoteridol from thermosensitive liposomes and could also indicate adequate temperature control. The next steps will be to investigate the effects of the release of gadolinium on the temperature map. They also hope to monitor perfusion of gadolinium and doxorubicin pharmacokinetics.

Brett Fite also discussed vascular permeability changes following copper doxorubicin released from temperature-sensitive liposomes as detected by dynamic contrast-enhanced MRI (DCE-MRI). Previous research demonstrated that doxorubicin temperature-sensitive liposomes and hyperthermia caused tumor regression in vivo. The objectives of the study were to evaluate DCE-MRI as a method to visualize doxorubicin release from temperature-sensitive liposomes. There were significant changes in the shape of the DCE-MRI curve observed 30 minutes following treatment due to changes in vascular permeability. There was an overall increase in the volume transfer coefficient (vt). Fite concluded that DCE-MRI may provide efficacy feedback.

Brett Fite also spoke on ultrasound ablation to transiently increase accumulation of small molecule gadoteridol within the ablated volume. The objective of this study was to evaluate the extent to which small molecules can be delivered to a tumor following MR-guided FUS ablation. In vivo studies showed that gadoteridol accumulation started within 5 minutes and continued to increase over the following hour. The effect peaked at 90 minutes, but some accumulation continued over 6 hours. These results suggest that small molecules can be delivered to tumors post-ablation.

Cardiovascular

Presentations highlighted the use of FUS for a variety of applications in the treatment of cardiovascular disease including histotripsy for thrombolysis, renal denervation, cardiac ablation, and cardiac pacing.

Zhen Xu from the University of Michigan presented on noninvasive thrombolysis using microtripsy in a porcine deep vein thrombosis model. Histotripsy uses short pulses of ultrasound to break down blood clots via cavitation. There was some concern that the shock scattering mechanism of histotripsy could damage the vessel wall. The intrinsic threshold mechanism (microtripsy) uses a single 1 second pulse and removes the shock scattering method. Microtripsy can generate and confine cavitation in the vessel lumen during thrombolysis treatment, resulting in precise recanalization with minimal vessel damage. This was tested in an in vivo animal study (pigs). Results showed that cavitation was well-confined in the vein lumen during all treatments. No pre- or post-focal cavitation was observed. Flow was improved and restored in 13 out of 14 treatments. No severe hemolysis was observed in any of the treatments. Only minimal hemorrhage outside the treated veins was observed.

Allison Payne of the University of Utah presented an investigation of the acute blood pressure response during FUS bilateral renal denervation in a normotensive rat model. Assessments were invasive blood pressure measurements, quantitative T1 maps, and MR thermometry. Eleven Sprague-Dawley rats were treated with eight sonications per animal at 2 W for 20 seconds. Animals were monitored for 30 days prior to being euthanized. Results demonstrated transient decreases in mean arterial pressure in 11 of 36 sonications. At 30 days after treatment, norepinephrine in kidney medulla was reduced by 36%. The study supported the use of MR-guided FUS for renal denervation, demonstrating that it is both safe and effective. MRI was able to provide real-time monitoring of the procedure. The next steps will include studies in a hypertensive animal model, and of the optimization of ultrasound parameters.

Cyril Lafon from INSERM spoke on the use of transesophageal HIFU for cardiac ablation in nonhuman primates. The goals of the study were to demonstrate the feasibility of transesophageal HIFU-induced thermal ablation in the heart in a realistic animal model (nonhuman primate) and to evaluate passive elastography as a monitoring technique. A transesophageal echocardiography (TEE) transducer was used in the experiments in baboons. Results suggest that transesophageal HIFU in cardiac tissues is feasible to induce thermal damage and is safe. Passive elastography was feasible for detecting thermal damage.

Bruno Quesson from the University of Bordeaux described ex vivo and in vivo noninvasive ultrasound-based cardiac pacing. A multimodal approach (ultrasound, MRI, and electrophysiology) was used in the experimental setup. Ultrasound stimulation was used to induce cardiac pacing. Results demonstrated that noninvasive cardiac stimulation and pacing with FUS was feasible. Further studies are required to better characterize the mechanisms depending on sonication parameters. Safety assessments are also needed for longer durations. Real-time image guidance will also be necessary going forward.

Joe Frank from the National Institutes of Health described restoring perfusion after critical hindlimb ischemia using pulsed FUS and mesenchymal stem cells (MSCs) in an aged mouse model. The objectives of the study were to use pulsed FUS to prime muscle tissue prior to administering MSCs. Proteomic analysis showed elevations of IL-17 and other inflammatory factors. When pulsed FUS was used in conjunction with MSCs, cell trafficking and perfusion to the ischemic limb increased compared to treatment with MSCs alone. There was a statistical increase in limb reperfusion between pulsed FUS and MSCs versus MSCs alone when treatment was initiated at day 14 post-external iliac ligation in old mice. There was also an increase in CD31+ cells in the combined approach. Frank concluded thatin vivo preconditioning by pulsed FUS is a novel approach to cell therapy.

Michael Gertner of Kona Medical, Inc. presented on using an ultrasound image guided therapeutic system for noninvasive renal nerve ablation. Kona medical has developed a commercial ultrasound-based imaging/therapeutic system for noninvasive treatment of hypertension and other disorders. Preclinical studies evaluated safety and efficacy in pigs. Virtual acoustic patient models were used to perform experiments modeling the

actual procedures that will be used in clinical trials. The technology platform has been designed to image, target, track, and treat moving tissue. The device has been granted an FDA IDE. Pilot clinical trials will provide initial indication of safety and efficacy, and randomized clinical trials are currently underway.

Women's Health/Gynecological

Several presentations highlighted the use of FUS for the treatment of uterine fibroids.

Young-sun Kim of Samsung Medical Center spoke on the preservation of endometrium after MR-guided HIFU ablation for submucosal uterine fibroids. Endometrium integrity after MR-guided HIFU ablation of fibroids in 101 women was retrospectively evaluated, along with associated risk factors for injury. Sonalleve MR-guided HIFU Therapy System (Phillips Healthcare was used for treatment. In most cases MR findings confirmed that the endometrium was preserved and intact after HIFU ablation of submucosal uterine fibroids. Injured endometrium was more frequent after treating endometrial-protruded fibroids, yet the injury usually recovered spontaneously.

Young-sun Kim also presented results on the use of GnRHa as a pretreatment for MR-guided HIFU ablation of uterine fibroids. The study evaluated the change in fibroid volume and fibroid T2 S1 ratio after using gonadotropin-releasing hormone analogs (GnRHa) as a pretreatment for MR-guided HIFU ablation, and it sought to determine the significant influencing factors for favorable changes after ablation. Women (N=60) received GnRHa pretreatment via subcutaneous injections. Fibroid volume significantly decreased with treatment. After GnRHa pretreatment of HIFU ablation, uterine fibroids with higher T2 S1 and/or greater wash-in rate showed a greater volume reduction, which was strengthened by additional cycles of GnRHa. T2 signal intensity of fibroids showed variable and non-specific changes after GnRHa therapy.

Joanne van Breugel from the University Medical Center Utrecht presented on targeted vessel ablation with MR-guided HIFU for the treatment of type 3 uterine fibroids. Type 3 fibroids have a high signal intensity on T2 images and they have a higher or equal signal to myometrium, a high perfusion, and a high extracellular volume content. A new treatment approach was developed using MR-guided HIFU for targeted vessel ablation. The approach included targeted vessel ablation with a high power (450 W) to decrease perfusion, followed by typical sonications (<300 W) to debulk. Targeting of vessels with high-power sonications proved difficult. The team added dynamic contrast-enhanced scans directly prior to HIFU treatment to overcome the fact that the non-perfused volume is larger than the treated volume. This new approach led to ablation in most patients.

Jae Young Lee from Seoul National University Hospital spoke about a 2-year prospective clinical trial for treatment of uterine fibroids using a portable ultrasound-guided HIFU system with 3D electronic screening and targeting forecast function. A prospective study was carried out to investigate the clinical efficacy and safety of the portable HIFU system for the treatment of uterine fibroids. Tumor volume decreased after treatment, pain significantly decreased, and quality of life scores improved. In summary, ultrasound-guided treatment of uterine fibroids using this portable system was safe and effective.

Dandan Zhang from the Hospital of Harbin Medical University spoke on a preliminary clinical evaluation of MR-guided HIFU combined with GnRHa therapy in the treatment of adenomyosis, a condition with inadequate treatment options. They retrospectively assessed nine patients that were treated for adenomyosis. MR-guided HIFU alone improved clinical symptoms and there were no complications or adverse events. However, there was one patient that relapsed, and a smaller non-perfused volume was obtained for diffuse adenomyosis. GnRHa therapy was added to the treatment to enhance ultrasound energy deposition. The addition of GnRHa increased the non-perfused volume ratio and decreased uterine volume. Zhang concluded that the addition of GnRHa therapy to MR-guided HIFU could improve efficacy, but further evaluation in a larger sample of patients is needed.

Susan Dababou and Christina Marrocchio from Sapienza University in Rome discussed a non-contrast method for evaluating non-perfused volume after MR-guided FUS treatment of uterine fibroids. The purpose of the study was to investigate whether the non-perfused volume accurately represents ablated tissue and whether a new predictive factor could be developed. The black line volume (BLV) was generated by manually drawing a black line contour on the hypointense contour margin of fibroids in non-contrast images. Five patients with follow-up imaging were included in the study. The BLV was calculated using magnitude images from MR thermometry acquired during sonication during the follow-up scan. Results suggest that the BLV represents the true ablated volume. The team concluded that BLV correlates well with the truly ablated region and the non-perfused volume. BLV was a better predictor because it excluded the ultimately reperfused volume. BLV may also be a powerful tool to reveal inadequately treated regions during the planning session of a second treatment, allowing a more tailored targeting and preventing under- or over-treatment.

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Musculoskeletal

Presentations highlighted the use of FUS for musculoskeletal applications including chronic wound healing, reducing pain from bone metastasis, and the treatment of osteoarthritis of the facet joints.

Ashish Ranjan from Oklahoma State University discussed HIFU for targeted antibiotic delivery and therapy of chronic wounds and osteomyelitis. Chronic wound therapy requires long duration treatment with antimicrobials as well as the systemic administration of drug to reach an infection site. Low temperature-sensitive liposome (LTSL) encapsulated ciprofloxacin was used as an antimicrobial in these experiments. Mild hyperthermia increases the release of ciprofloxacin from LTSLs. Rats were treated with either LTSL ciprofloxacin or free drug followed by 1 hour of muscle hyperthermia. Muscle tissue was analyzed for ciprofloxacin. The combination treatment of LTSL plus MR-guided HIFU significantly increased ciprofloxacin accumulation in muscle tissue. S. aureus biofilms were also treated with LTSLs with ciprofloxacin and hyperthermia. LTSLs treated with hyperthermia significantly improved killing of biofilm bacteria.

Hirofumi Namba of Kochi Medical School spoke on the effectiveness of MR-guided FUS pain relief in patients with bone metastasis or chronic osteoarthritis. FUS therapy can be used for ablation of sensitized nerve fibers at the bone surface. The aim of this study was to identify diseases (bone metastasis, lumbar facet osteoarthritis, and knee osteoarthritis) that could benefit from FUS. They also aimed to determine an optimal treatment site by finding the most tender points of the target lesion. The outcome measure was subjective pain and pressure pain threshold at the target lesion site. All groups had decreases in pain at 3 months and an increase in pressure pain threshold. Response to treatment tended to be better in pain from bone metastases than chronic osteoarthritic pain.

Antonio Bazzocchi presented on behalf of Mattia Squarcia from Hospital Clinic Barcelona on the effectiveness and safety of MR-guided HIFU for the treatment of osteoarticular lumbar spinal pain originating from the facet joints. In addition to assessing efficacy and safety, they also evaluated quality of life after treatment. Seven patients were treated bilaterally at the lumbar levels and each facet joint was treated with sequential sonications lasting for 10 to 20 seconds. Up to eight sonications per facet joint were completed. Real-time intraprocedural temperature monitoring was performed using thermal sensitive MRI sequences. There were no major complications and all patients reported less pain after treatment. Mean quality of life scores improved by 44% at 12 months post treatment. Preliminary results indicated that MR-guided HIFU is a valid tool that enriches the therapeutic options for chronic back pain caused by facet joint osteoarthritis.

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Emerging Applications

Presentations highlighted the potential use of FUS to treat various new indications including kidney stones, acute kidney injury, multiple sclerosis, and peripheral neuropathy.

Vera Khokhlova from the University of Washington discussed transcutaneous boiling histotripsy ablation of the kidney in an in vivo porcine model. The objectives of this study were to demonstrate the feasibility of in vivo volumetric, transcutaneous/transcostal boiling histotripsy treatment of kidney in a large animal model. A focal spot of 1 mm was sonicated with B-mode image guidance. The boiling histotripsy dose was 5 to 30 pulses per spot. Results demonstrated precise ablation. The relative sensitivity was similar to previous ex vivo experiments. There was no near-field heating or collateral damage, no gross hematuria, and connective tissue structures were spared, but small areas of petechial perinephric hemorrhage and collecting system clots were observed. Ultrasound-guided transcutaneous and partially transcostal boiling histotripsy ablation in kidney is feasible. Respiratory motion does not result in significant spreading of the lesion. They also found that treatment can be accelerated 10-fold by using shorter pulses of high amplitude.

Scott Burks of NIH discussed the use of pulsed FUS for enhancing MSC potency to improve acute kidney injury outcomes in an animal model (mice given cisplatin). Previous work has shown that pulsed FUS increases MSC homing to areas of damage. In vitro exposure of MSC to pro-inflammatory cytokines (IL-6, TNFα, and IFNγ) potentiated MSCs. Pulsed FUS increased renal IFNγ which stimulates MSC production of IL-10 to further improve MSC homing and improve renal function. Using an IFNγ knockout mouse model, MSCs still homed to the injury, but did not cause increased production of IL-10. Next the team used an IL-10 knockdown mouse and found that MSCs still homed to the site of injury and improved kidney function after injury. Burks concluded that renal IFNγ is not necessary for pulsed FUS-enhanced MSC homing to the site of acute kidney injury, which is an IL-10 dependent treatment mechanism. In vivo cell preconditioning by pulsed FUS is a novel approach to cell therapy with many implications for treatment of additional diseases in other organs.

Oleg Sapozhnikov from the University of Washington presented on the use of focused ultrasound beams for generating acoustic radiation force to push and trap kidney stones. Radiation force depends on the sphere radius (α) and the beam waist radius (α0). For the treatment of kidney stones, the radiation force is greatest when the beam width is close to the stone diameter. The direction of the force is also important. Modeling techniques included glass beads or Styrofoam beads to represent kidney stones. A single-element source was combined with a phase plate to create a vortex beam and tested with Styrofoam beads. The ultrasound vortex beam controlled the direction of Styrofoam beads in a preliminary experiment.

Pierre Mourad of the University of Washington discussed the use of modulated FUS for the treatment of de-myelinating axons in MS lesions in pilot animal studies. The aim of the research was to investigate whether FUS can be used to decelerate demyelination and accelerate remyelination of axons. Preclinical research demonstrated that FUS activation of MS lesions reduced demyelination and/or accelerated remyelination in a mouse model of MS (cuprizone). Myelin staining showed accelerated remyelination at the site of FUS application. Next, further histological analysis, MRI image analysis, and electron microscopy will be completed. An autoimmune model of MS will also be used for optimization of FUS treatment.

Matthew Downs of Columbia University presented the use of FUS for peripheral nerve stimulation in vivo. Peripheral nerve stimulation could be used to noninvasively treat neurological disorders such as peripheral neuropathy. The aim of the described studies was to identify FUS parameters to successfully elicit electromyogram (EMG) responses due to stimulation of peripheral nerves and to determine the safety of the technique through behavioral testing and histology. Downs was able to elicit muscle activation in vivo with FUS stimulation. Behavioral testing in an open field did not indicate any damage following FUS stimulation of the sciatic nerve. Additionally, histology did not indicate any damage to the muscle tissue. Muscle activation was confirmed to be specific to nerve stimulation by the lack of EMG response after the application of lidocaine. The next steps will be to develop real-time monitoring of FUS stimulation via ultrasound B-mode imaging and elastography.

Scott Burks also discussed molecular responses to pulsed FUS for stem cell homing through the mechanosensitive TRPC1 channel. The objectives of this research were to determine the physical properties of pulsed FUS that interact with tissue to drive pro-homing molecular responses. They in vestigated the molecular pathway from pulsed FUS in kidney and skeletal muscle. Results demonstrated that stretch—activated TRPC1 (voltage independent) was critical to the pulsed FUS molecular response. Voltage-gated calcium channels are also important.

Burks also presented on the use of low-intensity therapeutic ultrasound to prolong the survival of transplanted MSCs. MSCs are considered 'immune privileged', but usually only reside in the tissue for 3 to 10 days. The objectives of this study were to examine whether local microenvironment alterations could support MSC viability and prolong lifetimes. MSCs were directly injected into the hamstring of a mouse model, which were treated therapeutically with ultrasound on a daily basis. Overtime, MSC lifetimes were prolonged. The initial inflammatory response develops into an anti-inflammatory, pro-growth/pro-mitotic microenvironment. Proteomic responses indicate that there are many similarities between therapeutic ultrasound and pulsed FUS responses. Burks concluded that this therapy could be a potentially easy and cost-effective way to improve cell therapies.

Alexander Klibanov from UVA spoke on the use of red blood cells as ultrasound-triggered drug delivery vehicles activated via perfluorocarbon nanodroplets, targeting, and photoacoustic imaging. Red blood cells are alternative acoustic drug delivery carriers, with the advantage that they are specific to the patients themselves. Conventional delivery results in slow drug release by diffusion and a lack of spatiotemporal triggering. Droplets can be vaporized with ultrasound. Red blood cells can be loaded with acoustic droplets. Mouse model experiments demonstrated that magnetically targeted red blood cells can be photoacoustically tracked. Klibanov concluded that acoustically activated red blood cells are a feasible alternative for image-guided drug delivery.

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Technical Topics

Calum Crake from Brigham and Women's Hospital discussed passive acoustic mapping and MR thermometry for real-time multi-modality imaging of FUS ablation. Although MRI provides excellent imaging and can map temperature, it cannot detect cavitation, which has significant implications for both safety and efficacy. The addition of real-time acoustic mapping could allow robust monitoring of both cavitation and temperature. An ultrasound array was combined with a FUS transducer inside the MRI in an animal model and a phase-shift nanoemulsion was injected to enhance cavitation. The experiments demonstrated that temperature rise and cavitation increase with power and exposure time. There was also good correlation between MRI thermometry and passive acoustic mapping. Real-time passive acoustic imaging and MR thermometry may be used simultaneously to improve monitoring of cavitation-enhanced tumor ablation. Phase-shift nanoemulsion may be used to enhance cavitation and therefore, also temperaturerise. The next steps will be to optimize these methods and control phase-shift nanoemulsion-enhanced ablation.

Satya Kothapalli from Washington University St. Louis presented on acoustic characterization of a clinical MR-guided HIFU system. Acoustic characterization would help to ensure safe, effective, and repeatable HIFU thermal ablation treatments. This study aimed to create an MR-compatible hydrophone system and methods. The system was designed for use with a Phillips Sonalleve V2 MR-guided HIFU. A fiber-optic hydrophone system was developed for use within the MRI bore. Clinical MR-guided HIFU acoustic fields were characterized within the MRI bore, and validated with measurements outside the MRI suite. Kothapalli concluded that this method can be adopted as a quality assurance tool for use with MR-guided devices.

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Thursday
September 1, 2016

The Journal of Therapeutic Ultrasound

Wady Gedroyc, Editor-in-Chief of the Journal of Therapeutic Ultrasound gave an update on the status of the journal and its mission. The goal is to make this the premier open access journal of therapeutic ultrasound. The journal has not yet received an impact factor; journals have to publish at least two papers per month for 12 months to achieve this. Once a paper is accepted it takes only 2 weeks to publish the paper. However, there is a large lag between submission and acceptance due to the slow review of papers by appropriate referees. The journal is working to reduce this time.

The Journal of Therapeutic Ultrasound aims to be the main journal in the FUS field. They are in need of submissions and need to publish more to achieve an impact factor. Without submissions the journal will not develop. The presenters at the Symposium were urged to submit their work to the journal. The journal will also be inviting many of the speakers to submit manuscripts. Gedroyc encouraged participants to contact him if they had any suggestions for areas of interest or review articles.

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Panel Discussion: Biomechanisms

Panel Moderator: J. Foley. Panelists: T. Bullock, K. Ferrara, N. McDannold, C. Moonen, Z. Xu.

The panel discussed their opinions on the following topics:

1. **Panelists were invited to share their current work on biomechanisms and their clinical utility.**
   Panelists discussed the tumor microenvironment, combining FUS with new therapeutics (such as immunotherapy), disrupting the BBB to deliver therapeutics directly to the brain, and identifying the optimal use for histotripsy

2. **In a combination approach with FUS and another therapy, how would FUS be used? Is it more of a first-line therapy or an adjuvant?**
   At this time, optimizing FUS is still in the early stages. Another issue is that even with treatment successes, it is still not widely accepted by the medical community, which prevents FUS from becoming a first-line therapy. In most cases, FUS would be an adjuvant, but with time hopefully can be developed into first-line treatments.

3. **What work still needs to be done to understand the mechanisms and safety for thermal ablation?**
   With ablation in the brain, there is still a lot of research that needs to be done to understand the mechanisms. There can be factors in patients that researchers did not anticipate based on animal models. The biomechanisms are not understood for histotripsy ablation, and there is very little data available from human patients. Cavitation appears to release anticoagulant factors that reduce bleeding in the body, but brain bleeding may be a problem. There are a lot of factors that still need to be investigated such as the effects of the immune system.

4. **What are the challenges in bringing FUS to the clinic, and what can we do to combat some of these challenges?.**
   Some in the neuroscience community feel that we should not open the BBB. However, there is a history of opening the BBB with mannitol. Additionally, safety studies in humans have shown that this is a safe procedure. McDannold suggested that a dialogue with skeptical groups of researchers could help to address these concerns. Determine what data could convince them, and then provide that data.

5. **What are your thoughts on collaboration, particularly in communities outside of the FUS community?**
   There was a suggestion that some collaborations should be strategically done in specific areas that will have the biggest impact. Consider the end users of the device, and reach out to those particular groups. Also engage more biologists to help answer mechanistic questions.

6. **What are some of the challenges in moving this research forward?**
   The time necessary for studying the long-term effects is prohibitive. It's been a slow transition to get thermal ablation into the clinic, particularly due to funding and regulatory issues. Another issue is that we do not understand the mechanisms of metastasis, particularly in the brain. Due to the novelty of FUS treatment for brain applications, it is difficult to translate the treatments to the clinic. It takes time to design clinical trials that will be successful.

7. **The panelists were invited to bring any important issues to the FUS community.**
   It is important to have a unifying journal, so that the research can be found in one place. It is also important to be transparent and share data and information to move the field forward. FUS researchers also need to reach out to other fields through conferences to increase awareness

8. **The discussion was opened up to the audience.**
   A representative from the FDA stated that it is important to present the data on both successes and failures. When they are evaluating a submission they need to know at which stage the device is in the development process. Standardizing results is also very helpful, so that studies can be compared.

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Collaboration and Data Sharing

The lack of data sharing and collaboration among scientists is hampering the research enterprise. Collaboration is key to avoid redundancies and develop new ideas. As a community, the culture needs to change. Additionally, funding agencies and journals will start requiring data sharing.

Robert Spekman from UVA discussed collaboration and innovation in the medical device sector. Relationships and alliances dominate the business landscape. Alliances are defined as close, collaborative relationships between two, or more, firms that join forces to attain a set of mutually agreed upon goals that the parties would have had difficulty achieving alone. Collaboration suggests a more open and trusting set of relationships than would typically be found in a transactional set of exchanges. Alliances should be built on strengths and complementary assets. There also needs to be a sense of interdependence, so that both parties are interested in helping each other. Over 50% of alliances fail. Barriers to innovation are the impact of indirect ties, a ratio of unintended/intended information, and academic tensions within industry. To form a successful alliance, there needs to be a governance. Placing a structure, reporting system, and incentive system will help to strengthen the alliance. Develop mechanisms for dealing with disagreements, inequitable results, and the eventualities of exit.

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Panel Discussion: Successful FUS Sites

Moderator: S. LeBlang. Panelists: J. Cochran, P. Ghanouni, B. Lang, T. Lozinski, C. Robertson.

Pejman Ghanouni shared some lessons learned from the FUS experience with uterine fibroids at Stanford University. Finding the right patient and the right fibroid for treatment with FUS is a key to success. One tip for reimbursement is to explain that the patient has already received all the treatments recommended by guidelines and they didn't work, and that FUS is being used as an alternative method. It is important to work closely with colleagues in multiple areas such as oncologists and anesthesiologists. It helps the patient if the anesthesiologist is an expert in regional anesthesia. At Stanford, one user treats all patients, and that person is the expert at using FUS. There is one device in use. They also established a fibroid center, where the patient sees multiple physicians and discusses various treatment options. The patient is directed to the best option for their particular situation. They have taken this model to open a desmoid center as well. There is also a centralized approach for developing new FUS applications, which is helpful for

getting new clinical trials started from both a funding and regulatory perspective. The advantages of clinical trials have been useful. They already have a team in place, so that when the device is approved there is already a system in place. Cost of the device can also be covered by research.

Tomasz Lozinski of the Pro-Familia Hospital discussed the development of a research center for non-invasive therapies. Over the past 18 months they have been treating uterine fibroids with HIFU. The total time for a patient procedure is approximately 220 minutes, which includes patient preparation and sonication time. Seventy-three percent of treatments achieved more than 50% ablation. The team is pursuing research into improving the treatment. First, they would like to decrease limitations and achieve manipulation of the fibroid away from the bowel. Second, they would like to increase the availability of HIFU for gynecologists. Thirdly, there should be more collaboration between radiologists and gynecologists to increase referrals for HIFU. Lastly, they are looking at whether there is a way to increase tissue sensitivity to HIFU such as oxytocin, misoprostol, or medoxryprogesterone.

Cary Robertson from Duke University spoke on the Duke experience with HIFU in prostate cancer treatment. Preliminary work in animal models was carried out at Duke to show efficacy of HIFU for the treatment of prostate cancer in the 1980's. Next, they developed a device that would work in human patients. The device was engineered to fit into the rectum, creates high-quality images for planning, creates high quality and reproducible ablation volumes, and avoids cavitation. The ENLIGHT clinical trial in low risk, low stage prostate cancer demonstrated reduced prostate volume and PSA. The results from this trial led to the FDA approval of HIFU for the treatment of prostate tissue ablation in October 2015. However, insurers have indicated that they need long-term follow-up data from North American patients to make decisions on reimbursement. HIFU research at Duke includes stakeholders from several different fields such as biomedical engineering, basic and clinical sciences. Robertson concluded that integrating HIFU into a multimodal or sequential therapeutic strategy for the treatment of prostate cancer is now a realistic goal.

The presentations were followed by a panel discussion on the following topics:

1. **What would it look like to have a dedicated HIFU center at your institution?**
   It would be exciting to be able to treat a variety of indications in one center. Training will be required. Having a dedicated magnet for the HIFU equipment is also necessary. Several panelists mentioned that the number of patients that can be treated is also dependent on reimbursement. If the only funding is from a research grant, that places more limitations on the number of treatments that can be performed.

2. **How do we handle the reimbursement issue with patients?**
   Robertson mentioned that reimbursement should be discussed as early as possible with patients. Ghanouni also mentioned that some procedures are more likely to be reimbursed than others. Another obstacle is that the reimbursement approval process can take 6 months or longer, when a different procedure may be easily reimbursed. However, Stanford has come up with a system that charges the patient the same price as their copay for the procedure upfront, and then reimbursement is submitted. If it is reimbursed, then the patient is refunded.

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Regulatory Science

Dawn Bardot from the Medical Device Innovation Consortium spoke on using regulatory science to increase patient access to new medical device technologies. The Medical Device Innovation Consortium is a 501(c)(3) public/private partnership collaborating on regulatory science to make patient access to new medical device technologies faster, safer, and more cost-effective. Bardot explained their partnership with the FDA to achieve a balance between pre-and post-market surveillance, design better clinical trials

through Bayesian statistical methodology, and include patient input. Patient preference information is important to inform clinical trial endpoints, inform subgroup considerations, and for labelling changes. Patient reported outcomes are important to monitor in the post-market situation and are of interest to payers, providers, and patients. Including patient preference information helps to ensure that the risk-benefit determination is patient-centric. Bardot gave an example that contrasted physicians and patients concerns regarding the decision to prescribe an anti-coagulation for atrial fibrillation; patients differed in their priorities for the risks and benefits of the treatment. Finally, a few examples of how to incorporate patient preferences into clinical trials and the regulatory process were discussed.

Panel Discussion: Evidence Building

Moderator: R. Williams. Panelists: T. Andreae, E. Blanc, M. Carol, and M. Ferre.

Randi Williams from KAI Research introduced the panel. She stated that there are four areas that must be achieved to be successful: approvals, acceptance, awareness, and adoption. The panel discussed the following topics with regard to evidence building for FUS

1. **Can you speak to the technologies that have gained approvals and the status of reimbursement for those technologies?**
   Mark Carol from SonaCare—they have two approved technologies, one for prostate cancer and one for laparoscopic ablation. Maurice Ferre from Insightec – the company focuses on three main areas: women's health, neurology, and oncology. They have various regulatory approvals throughout the world. Emmanuel Blanc from EDAP-TMS—they have one product for lithotripsy and one for HIFU (Ablatherm). They have several approvals including a 510K from the FDA for the Ablatherm for the ablation of prostate tissue. Thomas Andreae from Philips Healthcare—they have the Sonalleve HIFU system, which is in clinical trials for the treatment of uterine fibroids in the US and for other indications in Europe and Asia.

2. **How do you establish evidence to satisfy regulators, clinicians, and patients?**
   SonaCare established a concierge medical care system to coordinate the care of US patients to centers outside the US. With the concierge care, not only did patients go outside the US, but their clinicians traveled to these sites to learn HIFU technology. Ferre mentioned that the FDA will direct the design requirements of studies, and will require long-term data of the preliminary endpoints for at least one-year post-procedure. For brain applications, the FDA requires data confirming targeting of a specific brain region. It is important to design a regulatory-focused trial to accelerate approval. The next challenge is to get reimbursements; the bar keeps getting raised making reimbursement difficult. For future indications, they will work on reimbursement earlier. The patients also need to have a stronger voice with insurance companies to demand these procedures and get claims submitted.

3. **What sort of evidence is needed to convince insurers?**
   We need to perform the best clinical trials that we can, particularly comparative studies. However, patients are reluctant to enroll in a clinical trial where the options are an invasive surgical procedure versus a noninvasive outpatient procedure. The FDA has also been raising the bar over time, and now require clinical trials in the US population and other regulatory agencies also require clinical trials specific to their populations.

   Creating awareness among patients and politicians is necessary to push the issue with insurers. The work of the Foundation is helping. It's important to get patients to begin advocacy as well. The current regulatory environment has made it difficult for small and innovative companies to survive. Even in Europe, it can take years to get reimbursement for FUS.

4. **Are there any strategies that clinicians can use to get reimbursement**
   Ferre mentioned that a bill has been introduced in the US Congress proposing that FDA approval in and of itself, should be reasonable to get CMS reimbursement. There would a two-year trial period, which would allow clinicians to adopt the new technology. This is important from a policy perspective to accelerate development of innovative devices. Additionally, companies can start using health economic analysis to support applications to insurers.

Closing Remarks

Neal Kassell thanked the participants for contributing to the success of the Symposium. He predicted that in the next two years the field will mature. There will likely be a few new device manufacturers as well as consolidation. We are entering a new era of research where there will be more emphasis on data sharing and collaboration and new approaches to publication and results. We will also see greater adoption of FUS through increased awareness and reimbursement. Registries will contribute greatly to provide the data to show effectiveness. Upcoming meetings include the Winter School, ISTU, European Symposium, and the 6th International Symposium in 2018.

Awards

Ferenc Jolesz Memorial Award

Nathan McDannold, PhD

The Ferenc Jolesz Memorial Award was established in 2016 to honor the life of a true pioneer in focused ultrasound. The award, supported by Insightec, 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 Nathan McDannold, PhD.

Dr. McDannold is an Associate Professor in Radiology at Harvard University. Since 1996, he has worked in the Focused Ultrasound Laboratory at Brigham & Women's Hospital. His work has been devoted to the development and implementation of MRI-based thermometry methods and pre-clinical experiments testing MRI and ultrasound. In the clinical setting, his work involves treatments of breast tumors, uterine fibroids, and brain tumors. In recent years, he has been studying the use of ultrasound to temporarily disrupt the Blood-Brain Barrier, with the ultimate goal of targeted drug delivery in the brain.

"I am thrilled to receive this award in Ferenc's name," says McDannold. "He was always a great champion for not only the team here at the FUS laboratory at Brigham but also for the field overall. I am truly honored to be recognized by the Foundation and appreciate everything they have done to support ultrasound research."

Dr. McDannold will be acknowledged during the Sunday evening 10th Anniversary Gala Reception. He will deliver a presentation on his research on Monday morning. He also receives up to $5,000 toward Symposium registration, travel and lodging expenses and a $5,000 award.

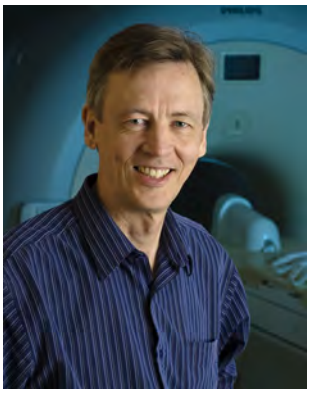
In Memoriam — Ferenc Jolesz, MD

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 non-invasive approach. He passed away suddenly in December 2014.

Ferenc 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 Ferenc's guidance, eventually leading to the FDA approval of a system to treat uterine fibroids and establishing the technology's potential to non-invasively treat a range of serious medical conditions. Ferenc spent the last few years championing the use of focused ultrasound for the brain, and was especially interested in exploring treating the ravages of Alzheimer's disease.

2016 Visionary Award



Kullervo Hynynen, PhD

Kullervo Hynynen, PhD

Pioneering physicist, Kullervo Hynynen, PhD, will receive the Focused Ultrasound Foundation's 2016 Visionary Award. This honor is given every two years at our Symposium and recognizes 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.

"I am very honored to receive this unexpected award," says Dr. Hynynen. "In the early days, when I would present at scientific meetings about the potential of focused ultrasound, it was quite discouraging when only a few people made up the audience. That certainly has changed with the recent clinical success, but I think that we are just scratching the surface of the potential of this technology. I have no doubt that focused ultrasound will become a major surgical tool and disrupt the way brain diseases are treated. The next few years will be very exciting for those who are involved in focused ultrasound research."

Dr. Hynynen has been conducting research in the field for more than 30 years, has over 300 publications, and was instrumental in the development of the first clinical system for MR-guided focused ultrasound. He currently leads a team of more than 50 engineers, scientists, students, and technicians who design and test systems, conduct preclinical studies, and facilitate clinical research at Sunnybrook and other hospitals in Toronto.

In Memoriam – Motti Zisser

Motti Zisser

In 2014, the Foundation's inaugural Visionary Award was presented to Insightec's Motti Zisser, and we were saddened by his passing earlier this year. The serial entrepreneur became the controlling investor of Insightec when he acquired Elbit Medical Imaging. After visiting Insightec and learning its mission, he became an exceptional supporter and advocate for the technology and was always looking for ways to minimize time from the laboratory to the patient bedside.

Motti was a unique combination of hard core businessman and a dreamer who wanted to improve the human condition. He and his wife, Dr. Bracha Zisser, established and operated a bone marrow bank and funded a hotel for children recovering from cancer. Motti's wish to help people coincided with his drive to accelerate everything within Insightec that could improve human health.

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 5th International Symposium on Focused Ultrasound.

Graduate students, research fellows, clinical fellows and junior faculty members are eligible to apply for the awards, which include complimentary event registration and up to an additional $2,000 in reimbursement for travel and lodging expenses.

Eleven Young Investigators are participating in the 5th International Symposium on Focused Ultrasound and being acknowledged in several ways.

Pre-Symposium Publicity
To emphasize the significance of the Young Investigator Awards, the Foundation announced this year's award recipients in our monthly e-newsletter.

Name Badges and Announcement
Award recipients have received unique name badges that indicate their status as Young Investigators.

Evening Poster Session and Young Investigator Spotlight
Young Investigators have a designated section of the Poster Hall. On Tuesday, 30 August 2016, during the poster session and reception, they will have an opportunity to showcase and present their work to the larger focused ultrasound community.

Matthew Adams

Awarded for: Endoluminal ultrasound applicators for thermal ablation of pancreatic cancer under MR-guidance: preliminary investigations in an in vivo porcine model [YI-1/P-YI-1]

Additional Presentation: Preliminary investigation of integrating deployable reflectors and fluid lenses with endoluminal ultrasound to enhance and dynamically adjust focal gain and depth [CA-20]

Matthew Adams is a graduate student in the University of California Berkeley—University of California San Francisco (UCSF) Graduate Program in Bioengineering and is working on his PhD dissertation in the UCSF Thermal Therapy Research Group led by Chris Diederich. His research focus includes the theoretical analysis and experimental development of catheter-based endoluminal ultrasound applicators for MR-guided thermal therapy of tissue targets adjacent to the gastrointestinal tract.

Aaron Bond, MD, PhD

Awarded for: A randomized, sham-controlled trial of transcranial MR guided focused ultrasound thalamotomy trial for the treatment of tremor-dominant, idiopathic Parkinson's disease [YI-2/P-YI-2]

Aaron Bond is a 6th year Neurosurgery resident at the University of Virginia. He has a PhD in Electrical Engineering with a special focus on semiconductor lasers with extensive research experience in academia and industry. As a Neurosurgery resident, he has conceptualized, led, and completed research projects involving large animal studies in convection enhanced delivery, and a human prospective clinical trial relating to Chiari malformations and intraoperative MRI imaging in addition to numerous retrospective studies. Recent work nearing completion includes a study on MRgFUS lesioning parameters and MRgFUS treatment of tremor dominant Parkinson's disease.

Joseph Corea

Awarded for: Acoustically Transparent Surface Coil Arrays for MR Guided HIFU [P-YI-10]

Joe Corea received his undergraduate degree in Microelectronic Engineering from the Rochester Institute of Technology (RIT) and is currently pursuing his PhD in Electrical Engineering at the University of California Berkeley. During his time at RIT, he was the Lead Electronics Engineer for the formula SAE race car. He has held positions in Process Engineering at IBM in East Fishkill, NY and Intel in Hudson, MA. He has also interned at GE Healthcare designing next generation hardware for MRI systems. Currently, he working on developing flexible MRI receive coils with Prof. Ana Arias. and Prof. Miki Lustig to be used in pediatric MR and HIFU therapies.

Colleen Curley

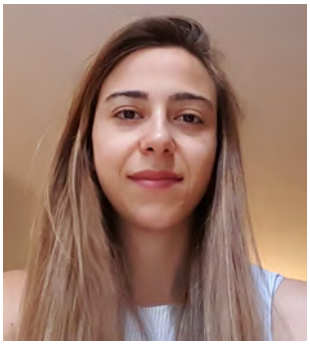
Awarded for: MR image-guided delivery of non-viral miRNA-34a gene vectors via focused ultrasound inhibits tumor growth in a mouse glioma model [YI-3/P-YI-3]]

Colleen Curley received her BS in Biology and MS in Bioengineering from Lehigh University in Bethlehem, Pennsylvania. She is currently pursuing a PhD in Biomedical Engineering at the University of Virginia in the laboratory of Dr. Richard Price.

David Hersh, MD

Awarded for: Pulsed ultrasound non-destructively expands the extracellular and perivascular spaces of the brain [YI-4/P-YI-4]

David Hersh received his bachelor's degree in biology from New York University in 2007 and went on to earn his MD from the NYU School of Medicine in 2011. He is currently a senior resident in the University of Maryland School of Medicine's Department of Neurosurgery, and is a member of the University of Maryland Translational Therapeutics Research Group. Working with Dr. Graeme Woodworth, Dr. Victor Frenkel, Dr. Anthony Kim, and Dr. Jeffrey Winkles, he is exploring the effect of pulsed ultrasound on the extracellular and perivascular spaces of the brain.



Maria Eleni Karakatsani

Awarded for: Neurorestoration of the nigrostriatal pathway through multiple treatments with FUS-facilitated brain drug delivery [YI-5/P-YI-5]

Maria Eleni (Marilena) Karakatsani is a rising third year PhD candidate in Elisa Konofagou's laboratory at Columbia University. She obtained her Bachelor's degree in Chemical Engineering from the National Technical University of Athens in Greece. Afterwards, she moved to the US to pursue a Master's degree in Biomedical Engineering at Rutgers University. Her thesis was on the behavioral differences in illusionary perceptions between Schizophrenia patients and healthy controls. Ever since she joined Konofagou's lab, she has been working on the focused ultrasound technology. She is utilizing FUS both as a therapeutic means that opens the Blood-Brain Barrier and facilitates drug delivery, but also as a treatment for transgenic animal models with proteinaceous aggregations. Currently, she is concluding her study in drug delivery to Parkinsonian mouse brains before switching gears to Alzheimer's models.

Maayan Kimhy

Awarded for: Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS) Treatment of Osteoid Osteoma: a Prospective Development Study [YI-6/P-YI-6]

Maayan Kimhy is currently starting her 6th year as a medical student in La Sapienza, Rome. During her army service in the Israeli defense forces (IDF), as a pre-paramedic soldier, she learned of her passion for the field of medicine. She is working on her thesis at the Imperial College of London, focusing on investigating expression patterns of cytokines and lymphocytic infiltration markers in young women with endometrial adenocarcinoma.

Zsofia Kovacs, PhD

Awarded for: Long-term effects of Blood Brain Barrier opening with pulsed Focused Ultrasound and microbubbles [YI-7/P-YI-7]

Additional Presentation: Sterile inflammatory response (SIR) in the brain following exposure to low intensity pulsed Focused Ultrasound and microbubble infusion [BR-15]

Zsofia I. Kovacs received her doctoral degree in Neuroscience from the Swiss Federal Institute of Technology in Zurich (ETHZ) with intensive oncology training at the University Children's Hospital Zurich. She joined the laboratory of Dr. Joseph A. Frank at the Department of Radiology and Imaging Sciences, National Institutes of Health as a postdoctoral research associate. Her research project involves using multivariate imaging, proteomic, and histopathological methodologies to gain a better understanding of the effects of pulsed Focused Ultrasound and microbubbles in the brain.

Matthew Silvestrini

Awarded for: Activatable nanodelivery combined with CpG-ODN and anti-PD-1 achieves a complete response in directly-treated and contralateral tumors in a murine breast cancer model [YI-8/P-YI-8]

Matthew Silvestrini is a graduate student in Dr. Katherine Ferrara's lab at the University of California-Davis. Matthew received his BS in Chemical Engineering and Chemistry from the University of Minnesota-Twin Cities. His research interests are in the area of immunotherapy, drug delivery, medical devices and translation medicine. Currently, he works on developing noninvasive strategies for cancer treatment by combining local ultrasound therapy with immunotherapy.

Bryant Svedin

Awarded for: Multi-echo Pseudo-Golden Angle Stack of Stars Thermometry with High Spatial and Temporal Resolution [P-YI-11

Bryant Svedin is a Physics PhD candidate at the University of Utah. He is currently investigating MR Thermometry techniques for use with FUS. His work has included the implementation and evaluation of tracking coils for predicting the location of the focal spot without test heating. He also demonstrated the use of phase navigator echoes for eliminating respiratory-caused ghosting artifacts in breast thermometry. He has been developing a new method for measuring temperature in both water and fat in the breast based on a stack of stars (hybrid radial/Cartesian) acquisition method that uses multiple high bandwidth echoes.

Frank Wolfram, MSc, PhD

Awarded for: Towards FUS Lung Cancer ablation, aspects of MR guidance in flooded lung [YI-9/P-YI-9]

Additional Presentation: Trans-pulmonary FUS ablation of liver using lung flooding, aspects of lung penetration and diaphragma motion [P-CA-75]

Frank Wolfram is working at the Lung Cancer Center of the SRH Wald-Klinikum Gera, Germany. In 2000, he received his MSc in Biomedical Engineering/Medical Physics at the Technical University of Ilmenau, Germany. After working in ultrasound technology for nearly a decade, his interests changed to medical applications of ultrasound. Recently, he received his PhD with Summa Cum Laude, from the Friedrich Schiller University Jena, Germany. His dissertation examined the basics of FUS Lung Cancer treatment using One Lung Flooding.

FUS Foundation Internship Programs

Claude Moore
CHARITABLE FOUNDATION

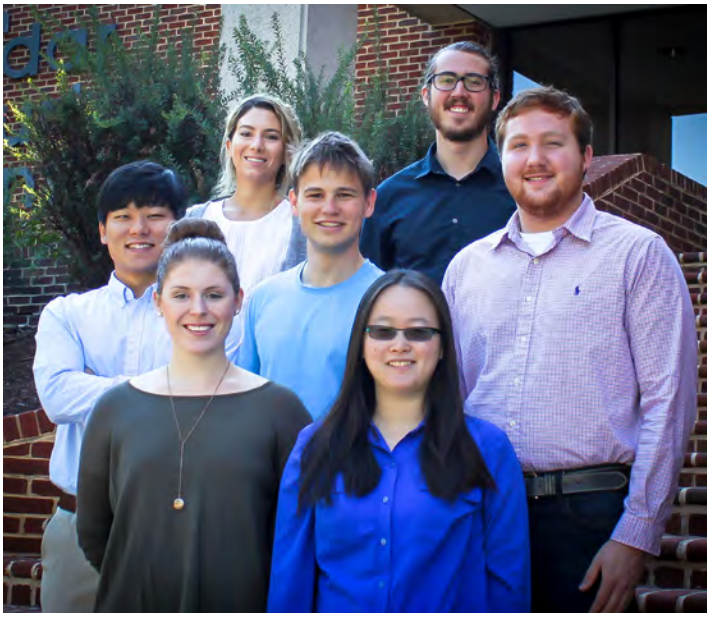
Summer Internship Program

The Focused Ultrasound Foundation's Summer Internship Program was established in 2012 with a 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 pre-clinical, clinical and business challenges. The program cultivates enthusiasm for focused ultrasound among the interns who then become invaluable ambassadors for the technology within their universities and the scientific community.

In the summer of 2015, the Foundation welcomed nine interns who worked on projects spanning from technical research to communications to assessing how the technology fits into the evolving healthcare environment.

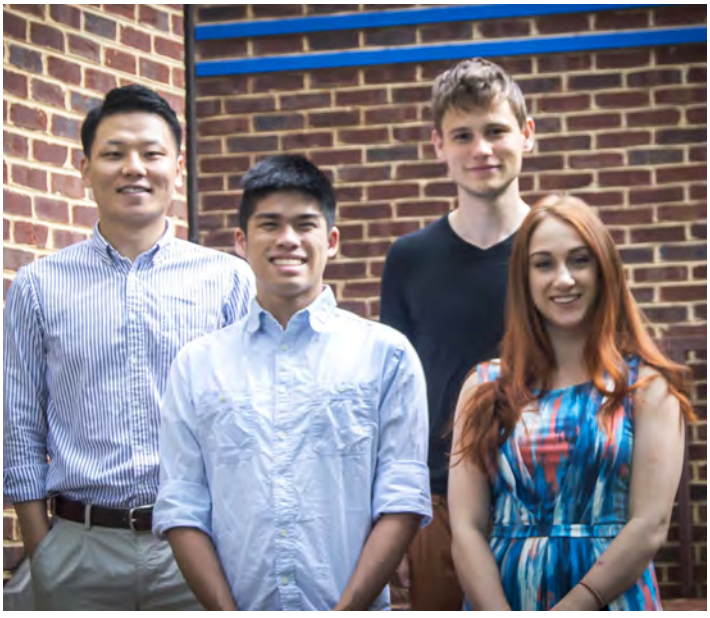
Two of these interns have returned this summer, and they are joined by a couple of new faces. This year, they are employing 3D printed techniques to develop a therapeutic ultrasound system, which will be used in a Foundation-funded sonodynamic therapy research project at the University of Virginia.

The intern program is generously funded in part by the Claude Moore Charitable Foundation (CMCF) and has been named in honor of Dr. Claude Moore, a physician and philanthropist who established the foundation before his death in 1991. The Claude Moore Focused Ultrasound Internship Program supports Dr. Moore's passion for developing academic excellence and



2015 Summer Interns

Back, left to right: Paige Calodney, Zack Larrabee
Middle, left to right: Changzhu Jin, Guillaume Maimbourg, Eric Ott
Front, left to right: Madison Stanley, Alexis Xu
Not pictured: Alexandra de Olazarra, Anders Quigg



2016 Summer Interns

Back, left to right: Changzhu Jin, Guillaume Maimbourg
Front row, left to right: Kevin Zeng, Helen Sporkin

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 will work in an established focused ultrasound laboratory under a researcher recognized in the field.

2015 Global Interns

Michael Breshock
University of Washington
Seattle, Washington, United States
Mentor: Tatiana Khokhlova, PhD

Susan Dababou
Stanford University
Stanford, California, United States
Mentor: Kim Butts Pauly, PhD

Nina Eckstein
University of Utah
Salt Lake City, Utah, United States
Mentor: Dennis Parker, PhD

Hans-Peter Erasmus
The Hospital for Sick Children
Toronto, Canada
Mentor: James Drake, MD

Manon Fraulob
INSERM
Lyon, France
Mentor: Cyril Lafon, PhD

Mikey Kimhy
University of Rome – La Sapienza
Rome, Italy
Mentor: Alessandro Napoli, MD

Guillaume Maimbourg
Institut Langevin
Paris, France
Mentor: Jean-François Aubry, PhD

Yash Majmudar
The Institute of Cancer Research
London, United Kingdom
Mentor: Gail ter Haar, PhD

Cristina Marrocchio
Stanford University
Stanford, California, United States
Mentor: Kim Butts Pauly, PhD

Paolo Massa
University of Rome – La Sapienza
Rome, Italy
Mentor: Alessandro Napoli, MD

Hailey McLean
University of Utah
Salt Lake City, Utah, United States
Mentor: Allison Payne, PhD

Sam Morris
Brigham and Women's Hospital
Boston, Massachusetts, United States
Mentor: Nathan McDannold, PhD

Karan Nagaraj
University College London
London, United Kingdom
Mentor: Nader Saffari, PhD

Thai-Son Nguyen
University of Michigan
Ann Arbor, Michigan, United States
Mentor: Zhen Xu, PhD

Colin Price
University of Virginia
Charlottesville, Virginia, United States
Mentor: Richard Price, PhD

Constantinos Psyllis
Cyprus University of Technology
Limassol, Cyprus
Mentor: Christakis Damianou, PhD

Ilia Sinilshchikov
Moscow State University
Moscow, Russia
Mentor: Vera Khokhlova, PhD

Irodotos Theocharous
Cyprus University of Technology
Limassol, Cyprus
Mentor: Christakis Damianou, PhD

Patricia Twilley
Vanderbilt University
Nashville, Tennessee, United States
Mentor: Charles Caskey, PhD

2016 Global Interns

Yulia Andriyakhina
Moscow State University
Moscow, Russia
Mentor: Vera Khokhlova, PhD

Hanna Bendjador
Brigham and Women's Hospital
Boston, Massachusetts, United States
Mentor: Nathan McDannold, PhD

Jessica Cahill
Brigham and Women's Hospital
Boston, Massachusetts, United States
Mentor: Nick Todd, PhD

Tianyi Chen
Vanderbilt University
Nashville, Tennessee, United States
Mentor: William Grissom, PhD

Mark Coelho
University of Maryland
Baltimore, Maryland, United States
Mentor: Rao Gullapalli, PhD

Jad El Harake
Vanderbilt University
Nashville, Tennessee, United States
Mentor: Charles Caskey, PhD

Emma Elson
The Institute of Cancer Research
London, United Kingdom
Mentor: Gail ter Haar, PhD

Nikolas Evripidou
Cyprus University of Technology
Limassol, Cyprus
Mentor: Christakis Damianou, PhD

Cecile Fant
INSERM
Lyon, France
Mentor: Cyril Lafon, PhD

Lewis Fausett
University of Utah
Salt Lake City, Utah, United States
Mentor: Dennis Parker, PhD

Lorenzo Giuliani
University of Washington
Seattle, Washington, United States
Mentor: Joo Ha Hwang, MD, PhD

Jannat Ijaz
The Institute of Cancer Research
London, United Kingdom
Mentor: Gail ter Haar, PhD

Kathleen Jedruszczuk
Memorial Sloan-Kettering Cancer Center
New York, New York, United States
Mentor: Elena Kaye, PhD

David Kittner
University of Maryland
Baltimore, Maryland, United States
Mentor: Rao Gullapalli, PhD

Yashasvi Matam
SonaCare
Indianapolis, Indiana, United States
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Pratik Mulpury
Stanford University
Stanford, California, United States
Mentor: Kim Butts Pauly, PhD

Marina Pavlova
University College London
London, United Kingdom
Mentor: Nader Saffari, PhD

Matteo Primavera
University of Washington
Seattle, Washington, United States
Mentor: Joo Ha Hwang, MD, PhD

Dmitry Sukhoruchkin
Moscow State University
Moscow, Russia
Mentor: Oleg Sapozhnikov, PhD

Receiving the highest peer-reviewed rating among submissions from the 2015 and 2016 FUSF Global Interns, Thai-Son Nguyen's abstract, entitled "Using Ray Tracing to predict Histotripsy Focal Shift in a Transcranial Setting," earned him travel support to attend and present his work at the Symposium.

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PHILIPS

Our MR-HIFU activities are concentrated in the MR-Therapy Business Unit located in Helsinki, Finland. We support our customers via global Philips Customer Services on a local level. Sonalleve MR-HIFU is approved for Uterine Fibroid and adenomyosis ablation and bone pain palliation in Europe and other countries.

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KAI Research, Inc. is celebrating 30 years partnering with pharmaceutical, biotechnology, academic, and federal clients to accelerate time to market for innovative drug treatments and medical devices. Our expert, customer-focused team supports phase I-IV trials and observational studies and provides pre- and post-marketing safety, pharmacovigilance, and medical communication services.

International Society for Therapeutic Ultrasound (ISTU)

www.istu.org
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Not exhibiting

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 arena for the benefit of patients worldwide.

Sonic Concepts, Inc.

www.sonicconcepts.com
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Sonic Concepts, Inc. manufactures high-power, wide-bandwidth ultrasound transducers and related equipment. SCI supplies single- or multi-element transducers, as well as annular, linear, and 2D arrays, transmit electronics, passive cavitation detectors, high-intensity hydrophones, radiation force balances, water degassing equipment, and more. SCI supports customer orders from initial prototyping into full-scale production.

Verasonics

www.verasonics.com
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Verasonics offers leading-edge capabilities for focused ultrasound research and development. The Vantage systems are real-time, software-based, programmable ultrasound platforms that provide flexible, precise imaging and HIFU including targeting, guidance, treatment, and monitoring.

Verasonics sells research systems and software to academic and commercial investigators, licenses its technology for commercial use, and provides consulting services. To learn more, visit us at: www.verasonics.com.

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www.alpinionusa.com

Alpinion Medical Systems believes that technology is only meaningful when it delivers value to health care providers. Guided by this philosophy Alpinion focuses on the development and production of ultrasound including diagnostic ultrasound and advanced piezoelectric and single-crystal transducer technology.

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Brainlab develops, manufactures and markets software-driven medical technology, enabling access to advanced, less invasive patient treatments.

Brainlab technology powers treatments in radiosurgery as well as numerous surgical fields including neurosurgery, orthopedic, ENT, CMF, spine and trauma. Founded in Munich in 1989, Brainlab has over 9000 systems installed in about 100 countries.

EDAP Technomed, Inc.

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EDAP TMS (NASDAQ: EDAP) markets today the Ablatherm® Robotic HIFU device for high-intensity focused ultrasound (HIFU) for prostate tissue ablation in the U.S. and for treatment of localized prostate cancer in the rest of the world. HIFU treatment is shown to be a minimally invasive and effective option for prostatic tissue ablation with a low occurrence of side effects. Ablatherm is generally recommended for patients with localized prostate cancer (stages T1-T2) who are not candidates for surgery or who prefer an alternative option, or for patients who failed radiotherapy treatment. The Company also produces and distributes the Sonolith® i-Move lithotripter for the t reatment of urinary tract stones using extra-corporeal shockwave lithotripsy (ESWL). For more information on the Company, please visit http://www.edap-tms.com, and http://www.hifu-planet.com.

Electronics & Innovation, Ltd.

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Electronics & Innovation Ltd, E&I, is a world leader in providing rugged and reliable RF power amplifiers. E&I designs and manufactures RF broadband power amplifiers, phased array systems, impedance matching and variable transformers, and CUSTOM RF solutions. In addition to our standard product lines, we are now offering custom modules and pallets—designed specifically to fulfill your OEM requirements. Operating globally and continuing to expand our technology, E&I is committed to providing RF power solutions of the highest quality, durability and ruggedness.

EUFUS - European Focused Ultrasound Charitable Society

www.eufus.org

EUFUS is a research and education organization serving as a philanthropic forum to estabish research funding, sharing experiences, reviewing best practices and promoting cooperation in the field of Focused Ultrasound for better patient treatment. Next scientific conference will take place in Leipzig/Germany, October 19–20, 2017.

Fibroid Relief

www.fibroidrelief.org
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Fibroid Relief is the patient advocacy initiative of the Focused Ultrasound Foundation. Since 2008, we have been dedicated to educating women suffering from uterine fibroids on their diagnosis and the various treatment options available.

Exhibitors and Supporters continued

FUS Foundation

www.fusfoundation.org
6th International Symposium: page 63
Board of Directors: page 64
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FOCUSED ULTRASOUND FOUNDATION

The Focused Ultrasound Foundation is a medical technology research, education and advocacy organization dedicated to improving the lives of millions of people with serious medical disorders by accelerating the development and adoption of focused ultrasound. The Foundation works to clear the path to global adoption by organizing and funding research, fostering collaboration, building awareness at our various workshops and symposia, and cultivating the next generation through internships and fellowships.

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University of Dundee

www.dundee.ac.uk

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TRANS-FUSIMO (Focused Ultrasound in Moving Organs) aim to combine MRI-guidance and monitoring technology with high intensity focused ultrasound (HI-FUS) energy to visualize tumours and surrounding anatomy and the subsequent thermal ablation of diseased tissue in surgical environments.

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Vituro Health provides comprehensive prostate care, empowering men during all stages of life. We enable our partner physicians to offer therapy through High Intensity Focused Ultrasound (HIFU), a new, FDA-approved, minimally invasive procedure that yields maximum efficacy with reduced recovery time and fewer side effects. For more information visit www.viturohealth.com

Partners

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The Israel-U.S. Binational Industrial Research and Development (BIRD) Foundation's mission is to accelerate growth through strategic partnerships. The BIRD Foundation promotes and facilitates collaboration between U.S. and Israeli companies in various technological fields for the mutually beneficial purpose of developing and commercializing promising innovations for the global market. Providing conditional grants of up to 50% of a joint project budget, the BIRD Foundation assists companies by identifying potential strategic partners in either Israel or the U.S. and facilitating introductions. In almost 40 years since its inception, BIRD has funded over 900 projects worth $10 billion in direct and indirect investment. Some of the recent collaborations that have matured into successfully commercialized products include ReWalk™, Poise™, Hockey IntelliGym™; OnVu™ and many more.

Cancer Research Institute

www.cancerresearch.org

The Cancer Research Institute is motivated by a very simple but important scientific fact: the human body has the ability to defend itself from cancer. The mission is straightforward—Save more lives with cancer immunotherapy. Our founding scientists believed that the key to long-term survival lay in learning how to manipulate the immune system to strengthen its defenses against cancer. We set out more than 60 years ago not only to prove this could be done, but also to do something with this knowledge that would truly help cancer patients. This work is now beginning to pay off: immunotherapies are transforming cancer treatment and bringing us closer to cures for all cancers.

Epilepsy Foundation

www.epilepsy.com

The Epilepsy Foundation and affiliates provide information and referral assistance; maintain individual and family support services; serve as advocates for the rights of those with epilepsy; and offer community-based education to employers, emergency first-responders, school nurses, and other allied health professionals.

International Essential Tremor Foundation

www.essentialtremor.org

The mission of the International Essential Tremor Foundation (IETF) is to provide global educational information, services and support to children and adults challenged by essential tremor (ET), to their families and health care providers, as well as to promote and fund ET research.

Partners continued

Melanoma Research Alliance

www.curemelanoma.org

The mission of the Melanoma Research Alliance (MRA) is to end suffering and death due to melanoma by collaborating with all stakeholders to accelerate powerful research, advance cures for all patients, and prevent more melanomas. We are the largest private funder of melanoma research. Since its founding in 2007, MRA has committed more than $79 million in funding to advance our understanding of this disease. MRA funds projects in the areas of prevention, diagnosis, and treatment, with the majority of funding allocated for melanoma treatment.

The Michael J. Fox Foundation

www.michaeljfox.org

or Parkinson's disease and improved therapies for those living with the condition today. As the world's largest nonprofit funder of Parkinson's research, the Foundation manages an aggressively funded research agenda. The Foundation works to ensure the patient voice is at the center of our efforts with one urgent goal in mind: Accelerating breakthroughs patients can feel in their everyday lives.

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Fibroid Relief

educating women about non-invasive treatment options

Fibroid Relief is the patient advocacy initiative of the Focused Ultrasound Foundation. Since 2008, we have been dedicated to supporting women suffering from uterine fibroids who seek non-invasive treatment alternatives, like focused ultrasound.

We reach more than 70,000 women annually via our website and social media, providing a platform for conversation and access to useful tips and tools.

We offer resources to educate women about fibroids, encourage early treatment to maximize choices like focused ultrasound, inform them of clinical trials and treatment sites, and provide tips for gaining insurance coverage.

FIBROID *Relief*

educating women about non-invasive treatment options

"Focused ultrasound had the fewest drawbacks for me and gave me the most hope."

-Elizabeth, fibroid patient

www.fibroidrelief.org facebook.com/fibroidrelief twitter.com/fibroidrelief

Funding Available for Focused Ultrasound Research

Grants of up to $100,000 for 12-month projects

The Foundation's **External Research Awards Program** supports technical, pre-clinical, and pilot clinical 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.

Research award recipient Beat Werner, PhD

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6th International Symposium on Focused Ultrasound 2018

OCTOBER 21-25, 2018 | RESTON, VIRGINIA

fusfoundation.org/symposium

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Thank you!

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