6th International Symposium on Focused Ultrasound 2018

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Event Summary

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Focused Ultrasound Foundation

Contents

Welcome

Neal F. Kassell, MD

Founder and Chairman,
Focused Ultrasound Foundation

Former Co-Chair of Neurosurgery,
University of Virginia,
Charlottesville, Virginia

Neal F. Kassell, MD, Founder and Chairman of the Focused Ultrasound Foundation, welcomed over 400 participants to the Symposium. In the two years since the last symposium, major milestones were reached. The FDA approved focused ultrasound for the treatment of patients with Parkinson's disease whose main symptom is tremor. Clinical trials are underway for several new indications including immunotherapy (checkpoint inhibitor) combined with focused ultrasound for the treatment of patients with metastatic breast cancer, focused ultrasound ablative surgery for the treatment of patients with obsessive-compulsive disorder and depression, and focused ultrasound ablative surgery for the treatment of back pain. These advances have tremendous potential to improve human health. Kassell encouraged participants to learn, communicate, collaborate, and have fun.

Honorary Presentations

Pejman Ghanouni, MD, PhD

Honorary President

Assistant Professor,
Stanford University School
of Medicine

Honorary President's Address

Pejman Ghanouni, MD, PhD discussed the growth of focused ultrasound (FUS) from 2012 to 2018. There are a variety of treatments available at Stanford for diseases that range from uterine fibroids (fertility sparing procedure), painful bone metastases, soft tissue tumors (desmoid tumors), essential tremor, tremor-dominant Parkinson's disease, and prostate cancer (intermediate-risk focal disease). Over time, keys to success emerged using a center of excellence model:

- Meet an unmet clinical need
- Build a treatment plan
- Establish a referral pattern
- Manage reimbursements

Additional considerations include a large patient population, FDA approval, meeting evidence requirements (evidence from a randomized controlled trial), and ease of the procedure. Patients are evaluated by a team of experts including physicians, interventional radiologists, and MR specialists that discuss a range of clinical treatment options with the patient. This method helps to directly refer patients that could benefit from FUS. Without an established referral pattern, patients will often not elect to undergo FUS. For example, patients with bone metastases pain have many options and radiotherapy remains the standard of care.

If a procedure lacks good evidence from a randomized controlled trial, this will likely impact insurance coverage decisions. Evidence on the efficacy of FUS treatment for uterine fibroids is lacking, and it is difficult to get insurance coverage for this procedure. On the other hand, strong evidence from randomized controlled trials exists for pain from bone metastases, which has resulted in insurance reimbursement for this procedure. Ghanouni also mentioned that bone is easy to treat and can

be done by a trained technician. A comparative trial of FUS and radiotherapy for bone pain could increase the number of patients that receive FUS compared with radiation treatments.

Ghanouni suggested various applications for FUS that need randomized controlled trials for unmet needs. Particular areas of interest are liver tumors, pancreatic tumors, brain tumors, and Alzheimer's disease. Additionally, increasing education and training in neurosurgery, interventional radiology, and urology to train more experts in FUS procedures and whom can then become advocates for the technology at their own institutions would be beneficial. He also challenged the community to promote FUS to funding agencies and establish challenge prizes to increase awareness and research for FUS.

Ferenc Jolesz Memorial Award Presentation

Seung-Schick Yoo, PhD, MBA

Associate Professor,
Brigham & Women's Hospital,
Harvard Medical School,
Boston, Massachusetts

Seung-Schick Yoo PhD, MBA discussed low-intensity transcranial FUS for neuromodulation. Region-specific neuromodulation techniques may provide unprecedented opportunities for neurotherapeutics, including functional brain mapping. Both excitatory and suppressive effects can be achieved with neuromodulation. Early work in rats and rabbits demonstrated that FUS sonications in the motor area controlling paw movement and tail movement could move the corresponding limb. Thalamic suppression with FUS in a pentylenetetrazol (PTZ) rat model of epilepsy could suppress seizure activity. Cranial nerve stimulation (abducens nerve) with FUS in rats could move the eye. FUS neuromodulation in an outpatient setting is now technically feasible and non-thermal mechanical interactions appear to be the main effector, but the exact mechanisms need to be defined. Confounding factors, such as auditory effects, suggest caution with future experiments.

In humans, FUS stimulation of the somatosensory cortex can elicit tactile sensations. FUS combined with fMRI to the visual cortex could activate the visual system as well as limbic structures. Several innovations have been made over the years in FUS. There are now multi-array, single-array, and hybrid array transducers. Image-guided FUS with optical navigation and intraoperative magnetic resonance imaging (MRI) guidance have been developed. In terms of acoustic coupling, there are several methods in use including a water bath, cone-shaped stand-off, and flexible hydrogel. There are a variety of platforms and sizes of devices including magnetic resonance guided focused ultrasound (MRgFUS), cart-based systems, and portable devices for use with different species. Simulation software with finite element finite-difference time-domain FE/FTDT with semi-real-time computation has been developed. Targeting can be achieved with acoustic force radiation (ARFI). Multi-modal integration with EEG/fMRI/PET for evaluating neuromodulatory effects and TMS/tDCS can be used for conjunctive therapy.

There are several potential first-line therapeutic uses for neuromodulation including modulating level of consciousness, targeting verification for high-intensity focused ultrasound (HIFU) surgery, ameliorating major depressive disorder, ameliorating substance abuse, epilepsy suppression, and performance/cognitive enhancement. Improvements in techniques, simulation software, monitoring capabilities, and further understanding of the mechanisms are necessary to realize this potential. Clinical trials evaluating safety and efficacy are necessary to move the field forward.

Keynote Speakers and Special Guests

Gary Shapiro, President and CEO of the Consumer Technology Association (CTA), discussed the value of innovation to solve critical problems in health and medicine. Physicians, governmental bodies, and patients have different views on how to measure a technology. For physicians the focus is efficacy, for governmental bodies the focus is cost, and for patients the focus is patient comfort (side effects, inconvenience). Reimbursements and costs are driving factors for decisions and need to factor into the decision-making process. Healthcare costs are increasing every year, and will be increasingly important over the next decade. FUS technology is a better way of treating patients, and has the potential to be transformative. An important aspect of this is the potential to lower overall costs in addition to the potential for pain treatment options. Shapiro encouraged the continued expansion of FUS for medical applications because it has the potential to improve the status quo, and that is how progress happens.

Scott Whitaker, President and CEO of the Advanced Medical Technology Association (AdvaMed), in conversation with Jessica Foley, chief scientific officer of the Focused Ultrasound Foundation, talked about the current state of medical device technology. Value of a given treatment is not only reflected in the treatment itself, but in the lifetime of the patient and how they are affected. A treatment that is initially more expensive, but gets a patient back to their normal lives faster has a greater value to the patient and the healthcare system. For example, patients with diabetes wear insulin pumps with a continuous glucose monitor (sampling every 5 minutes). This has led to rare occasions of a finger prick to measure blood sugar and eliminated the need for an insulin injection.

Improvements at the FDA have decreased decision-making time considerably over the past few years, with a clear and transparent pathway toward approval. The next challenge is working with the Centers for Medicare and Medicaid Services (CMS) for reimbursement, as it currently takes 3 to 5 years to get reimbursement after FDA approval. AdvaMed is coordinating with CMS and FDA to create a clear path to reimbursement. For example, efforts are underway for FDA-approved breakthrough products to automatically get CMS reimbursement for a period of time. This allows companies to gather evidence within the CMS population, particularly concerning value and impact on the patient. AdvaMed provides a value framework that helps companies determine the evidence they need to prove value beyond just cost. Examples are quality of life, getting back to work, and the emotional and mental aspects of better treatment.

Mary Lou Jepsen, Phd, CEO and Founder of Openwater, discussed the development of a new imaging technology that will use a 3D camera for high resolution imaging deep within the body. Two-thirds of the world's population lacks access to medical imaging. Lowering the cost of medical imaging, without compromising quality, could be transformative. MRI machines require more than just the machine, including a stable supply of electricity. The goal of Openwater is to put the power of MRI into a wearable, such as a knit cap or bandage.

Light passing through the body can be used for imaging. The optics of the human body are varied. For example, blood absorbs red and infrared (IR) light while flesh scatters red and near IR light. Holography can descatter the light in the body. Holography captures the interference pattern between two or more beams of coherent light of the same color. New camera chip technology makes it possible to capture high resolution images very quickly. Software can allow imaging of small or large areas, for example specific areas of interest in the brain.

The imaging device will consist of camera chips, ultrasonic chips, and lasers. A small test system was created, and preclinical mouse experiments are underway to test the imaging device. It is possible to combine this imaging device with FUS. Further information on imaging and specs are forthcoming later in 2018. Machine learning and big data will be leveraged to make the price of a scan cheaper, making medical imaging more accessible.

Monday
October 22, 2018

Brain

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

Movement Disorders – Clinical

Presentations highlighted clinical research for FUS treatment of movement disorders, including essential tremor and tremor-dominant Parkinson's disease.

Diane Huss from the University of Virginia reported six-year outcome data from the first FUS for essential tremor pilot study in 15 patients. Thirteen of the original patients participated in follow up. Outcome measures were the same and included the clinical rating scale for tremor (CRST), the Quebec user evaluation of satisfaction with assistive technology (QUEST), physical performance test, and the patient global impression of change (PGIC) for patient satisfaction. Three patients had subsequent deep brain stimulation (DBS), and these patients were assessed after the device was turned off for 12 hours. The CRST score remained at around 50% at 6 years. After 6 years quality of life scores (QUEST) were good and 85% of patients were satisfied with their results (PGIC).

Ying Meng from Sunnybrook Health Sciences Centre and Toronto Western Hospital presented 2-year follow-up outcomes after MRgFUS thalamotomy for the treatment of essential tremor. Current treatment for essential tremor includes medication (propranolol and primidone), botulinum toxin injections, and surgery for medically-refractory patients. The advantages of MRgFUS for essential tremor include no need for skin incisions or implants, lesions have immediate effectiveness, and intra-procedural adjustments are possible. This study aimed to follow patients treated at Sunnybrook (N=37). Dominant tremor score increased over time, but remained significantly decreased at 24 months compared to baseline. After 2 years, 33% of patients had tremor improvement. Multivariable in ear regression suggested that age and lesion volume were significantly related to tremor score at 12 months. Complications were transient, and most had resolved by 12- and 24-months post-procedure. Additionally, there were no new complications..

Cesare Gagliardo from the University of Palermo discussed a case study of a patient retreated with MRgFUS thalamotomy for essential tremor. A 72-year-old right-handed man resistant to treatment underwent left-sided ventral intermediate nucleus (VIM) thalamotomy. Treatment resulted in an immediate and sustained disappearance of the contralateral upper limb tremor. However, after 6 months, the tremor had returned. Analysis suggested that the return of the tremor may be related to a reparative process mixed with partial ablation of the targeted area. Six months after the first procedure, the patient underwent a new left-sided VIM thalamotomy, with an immediate response in symptoms. In conclusion, retreatment was safe and effective. There were no technical issues encountered when focusing the beam in the targeted area. There are several open questions such as how blood products and scar tissue from previous procedures will affect additional procedures and the underlying mechanisms that caused the tremor to return.

Rao Gullapalli from the University of Maryland presented results from an investigation of the association between the tremor improvement score and changes in functional connectivity between the ablated VIM and the rest of the brain in patients with essential tremor (N=19) 1 year after treatment with MRgFUS thalamotomy. Tremor was significantly reduced and remained reduced through 12 months after treatment. Connectivity analysis was done using scores from the dominant hand. The lesion was identified on 24-hour post-procedure MRI images. A 6 mm sphere was placed on the estimated lesion location in the 1-year post-treatment rs-fMRI data and used as a seed for resting state functional connectivity (rs-FC) analysis. There were increased functional changes in areas associated with motor

function, particularly in the cerebellum and insular cortex. There were decreased functional changes in areas associated with motor control and visuo-motor function. More data from a larger sample of patients is needed to draw firm conclusions.

Raul Martinez-Fernández from HM CINAC presented on brain modifications resulting from unilateral MRgFUS thalamotomy for essential tremor to the cerebello-thalamo-cortical structural connectivity. Patients (N=24) underwent unilateral MRgFUS thalamotomy. Tractography analysis was performed by reconstructing three anatomical pathways: cerebello-thalamic, cortico-spinal, and medial lemniscus. Diffusion tensor imaging (DTI) was used to measure lesion borders and the researchers found a decrease in fractional anisotropy and axial diffusivity from baseline to 3 months post-treatment. In the cerebello-thalamic tract there was a reduction in fractional anisotropy within the lesion border as well as a reduction in the white matter below the motor cortex. There was an increase in mean and radial diffusivity in the white matter below the motor cortex. There was a correlation between the changes in the cerebello-thalamic tract and clinical outcome. A decrease in functional anisotropy along the neighboring cortico-spinal tract was found, but this didn't have any clinical relevance. There was no effect in the untreated side of the brain. Patients that developed instability had a lesion with a greater effect on the cerebello-thalamic tract and those that developed sensory disturbances had a lesion with a greater effect on the medial lemniscus tract.than DBS and comparable to stereotactic radiosurgery.

Giuseppe Kenneth Ricciardi from Verona University Hospital discussed cortico-spinal tract visualization with double inversion recovery (DIR) sequences for MRgFUS VIM thermal ablation for essential tremor. The cortico-spinal tract is not visible on conventional MRI. DTI tractography is a proposed visualization method, but it is expensive and time consuming. A series of case studies (N=8) evaluated the ability of DIR to depict the lateral border of the thalamus, isolate the cortico-spinal tract within the posterior limb of the internal capsule from the adjacent thalamus, and distinguish the cortico-spinal tract from post-ablation VIM hyperintensity and edema. The researchers were able to use 3D-DIR sequencing to improve visualization of the cortico-spinal tract with MRgFUS. Using this sequence may help avoid or predict the development of limb weakness after MRgFUS VIM thermal ablation. Additional work is necessary to correlate clinical and imaging findings in these patients.

Steven Allen from the University of Virginia presented on the use of diffusion-weighted MRI for visualization of the lesion immediately after MRgFUS thalamotomy for essential tremor. There is a need for immediate MRI visualization and differentiation of the lesion because thermometry and patient feedback are ambiguous or error prone. Currently, surgeons use T2 weighted imaging, but it may take 30 minutes or longer for edema to develop and this method only images edema and not tissue ablation. Diffusion imaging allows the visualization of tissue that has been thermally coagulated and better differentiation between edema and ablated tissue within 5 minutes of the procedure. There were several technical challenges. The coupling water bath creates an artificially large field of view that makes it difficult to perform high resolution diffusion imaging, and the cardiac pulsations of the brain can introduce signal loss. Additional challenges include the fact that some of the transducers create a great deal of inhomogeneity of the radiofrequency transmission field. Diffusion-weighted imaging has been used on two patients, with reasonable contrast. Further refinements to the technique will be necessary.

Francesco Sammartino from Ohio State University discussed longitudinal analysis of lesion microstructural changes after MRgFUS thalamotomy in patients with essential tremor. Diffusion-weighted imaging derived metrics have been used to quantify tissue changes in different pathological brain states. There are several challenges with estimation of diffusion metrics after FUS ablation including vasogenic edema and tissue inhomogeneity caused by blood products and cerebral spinal fluid contamination as a type of partial volume effect. Generalized q-sampling imaging is a model-free algorithm based on a new relationship between the diffusion MRI signals and the spin distribution function (SDF). The SDF represents a quantitative distribution of the spins undergoing diffusion

instead of a probability distribution of the diffusion displacement. Restricted diffusion imaging (RDI) was estimated from whole-brain images from 18 patients preoperatively, 1-day post-operative, and 1-year post-operative. RDI changes were detectable even at 1 year with no changes detectable on T2 weighted MRI. RDI values uniformly increased in the lesion area in all patients at 1 day post-operatively. RDI change had a higher area under the curve (AUC) when used to predict lesion size with receiver operating characteristic curves to examine the sensitivity and specificity at all possible cutoffs of lesion size.

Pejman Ghanouni from Stanford University presented on the effect of skull density ratio (SDR) on the efficacy and safety of MRgFUS thalamotomy for essential tremor. Skulls are very heterogeneous between patients. The SDR is calculated from pre-operative CT scans and predicts the difficulty of MRgFUS treatment; higher ratios predict easier treatments with fewer sonications and total energy. In the US clinical trial, the lowest SDR allowable was 0.40. Currently, many insurance policies dictate that patients with 0.45 or greater SDR can be treated. The goal of this analysis was to look at patients with a variety of SDRs and evaluate for treatment efficacy. A higher SDR predicts a higher likelihood of reaching an internal temperature of 54°C. However, most patients (32 out of 53, 60%) with SDR <0.45 still reached this temperature. SDR does not correlate with CRST at 1 year. A lower SDR does not predict a higher rate of adverse events, and there were statistically fewer adverse events in patients with SDR <0.45 (43%, 95% CI: 30-58%) compared with those with a SDR >0.45. In summary, patients with lower SDR can be treated with safety and efficacy

Na Young Jung from Yonsei University College of Medicine presented data from a phase I clinical trial of unilateral MRgFUS pallidotomy for Parkinson's disease (PD). The study included patients (N=10) with medically refractive dyskinesia dominant PD that were followed for 1-year post-procedure. Two patients dropped out of the study due to insufficient temperature rise or no visible lesion in the target area. Four out of eight patients experienced a high temperature rise (>50°C) that facilitated better clinical outcomes, but this didn't reach statistical significance due to the small sample size. There were two changes on neuropsychology testing, but these symptoms are typically linked to PD and is unknown if these were related to procedure or PD. Quality of life was slightly improved after the procedure. There were a few common minor side effects such as mild headache and pin site pain, and back pain. One patient developed dysarthria and right hemiparesis during sonication, but recovered completely within 2 days. There were improvements in the unified Parkinson's disease rating scale (UPDRS) part III and dyskinesia after MRgFUS pallidotomy. Both lesion volume and temperature rise were related to treatment effectiveness. There are many factors that affect transcranial energy delivery including SDR and skull volume, heterogeneity of the skull composition, the incidence angle to the skull, and other factors (brain tissue volume, thickness or composition of the scalp or subcutaneous tissues, and intracranial calcification). Further research and technical advancements are required to widen or clarify the clinical indications related to the skull and other issues.

Toshio Yamaguchi from Shin-Yurigaoka General Hospital spoke about bilateral MRgFUS ablation of the pallido-thalamic tract for PD. This was a preliminary case study in three patients. The target was the left pallido-thalamic tract, 1 mm ventral to the anterior commissure-posterior commissure (AC-PC) line and 9 mm left lateral to the midcommissural point. In the first patient the off-phase and painful dystonia were entirely gone, and rigidity improved bilaterally after 3 months follow up with an improvement in the UPDRS score. In the second case, rigidity improved, UPDRS score improved, and L-DOPA dose decreased. In the third case, the patient had no wearing off and dyskinesia decreased. L-dopa-induced dystonia with pain on the left side was gone, and rigidity improved. This patient had transient somnolence immediately after FUS, which resolved in a few days and was likely due to edema following the procedure. In conclusion, although these are preliminary case reports with a short period of observation, pallido-thalamic ablation with MRgFUS may be safe and effective for parkinsonian symptoms.

Mark Burgess from Columbia University presented on FUS-mediated anti-α-synuclein antibody delivery for the treatment of PD in a mouse model (A53T). The loss of dopaminergic neurons in the substantia nigra is a hallmark of PD pathology. Lewy bodies composed of α-synuclein accumulate in the brain and are thought to contribute to toxicity and neuronal cell death. Passive immunization of anti- α-synuclein antibodies in the brain is inefficient due to the blood-brain barrier (BBB). A 1.5 MHz ultrasound transducer was used to sonicate the mouse brain at a peak pressure of 450 kPa with 6.7 ms pulses for a total of 60 seconds with a target in the midbrain. Custom microbubbles were used for BBB opening combined with a dose of anti- α-synuclein at 50 µg for three weekly treatments. T2 weighted MRI was performed immediately post-sonication, followed by 1-month histology of the sonicated brain tissue. FUS-induced BBB opening combined with antibody resulted in a reduction of α-synuclein without a significant loss of neurons. Antibody alone was able to achieve α-synuclein reduction, but FUS enhanced the neuroprotective effect. Treatment had good safety based on T2 weighted MRI. Future work will assess neurorestorative effects of passive immunization in late-stage PD and determine the mechanism of antibody-aided α-synuclein reduction.

Sijia Guo from the University of Maryland discussed predicting lesion size during MRgFUS pallidotomy for PD. Lesions cannot be observed during treatment due to low image contrast caused partially by the water bath and the fact that it takes 24 to 28 hours for the lesion to develop. For essential tremor treatments there is a good correlation between the size of the 1-day lesion and the 51°C thermal thresholding area. A temperature model was created to predict PD lesion size based on MR thermometry and the five highest-temperature sonications and results were compared with the 1-day post-procedure T2 weighted MRI. Results were calculated from 13 patients. A good correlation was observed between the 1-day lesion size and the thermal threshold area (48°C). The reduction in lesion size from 1 day to 1 month on T2-weighted MRI was not predictive and did not correlate with any thermal thresholding area.

Marc Gallay from Sonimodul presented on technical strategies for MRgFUS in PD. Data from 31 procedures with MRgFUS pallido-thalamic tract ablation were analyzed. Over time the procedure has been optimized. A positive correlation between mean axial T2 lesion diameter immediately post-treatment and the mean 240 CEM thermal dose diameter, the mean axial T2 diameter 48 hours post-treatment and the mean 18 CEM thermal dose diameter, and the mean axial T2 diameter immediately post-treatment and 48 hours post-treatment was found. One patient was treated bilaterally because of symptom recurrence. This patient had improvement in symptoms and was not taking any medications after undergoing MRgFUS.

Dheeraj Gandhi from the University of Maryland presented on MRgFUS pallidotomy using 3D fast gray matter acquisition T1 inversion recovery (FGATIR) imaging fused with diffusion tensor MRI of the cortico-spinal tracts. Standard imaging techniques for functional neurosurgery use indirect targeting with either consensus-based coordinates or atlas-based targeting. These techniques do not consider the inter-individual variability in the structure and location of the Globus pallidus interna (GPi). 3D FGATIR allows good contrast between the basal ganglia and white matter fiber tracts. Thirteen patients with medically-refractory dyskinesia symptoms of advanced PD were included in the multicenter prospective clinical trial. 3D FGATIR sequence was co-registered and fused with tractography images of the pyramidal tract and imported into the InSightec MRgFUS workstation and composite images were used for treatment planning. Post-operative day 1 images were independently reviewed by two experienced neuroradiologists and differences resolved with consensus. All patients underwent successful treatment of GPi and demonstrated significant improvement of their clinical symptoms. FGATIR imaging reliably demonstrated the boundaries of the Globus pallidus as well as the lamina between GPe and GPi in all patients. Locations of the optic tracts and the cortico-spinal tracts could be confidently inferred from the fused images and helped in guiding the ablation of GPi while avoiding lesion encroachment on to the optic and motor tracts. There were no serious adverse events; one

patient developed dysarthria that resolved to baseline within 3 months. In conclusion, the use of FGATIR imaging allows direct targeting of GPi motor territory as it reliably demonstrates the boundaries of Globus pallidus and presents excellent spatial and contrast resolution. Superimposition of pyramidal tract on FGATIR images may add to the safety of FUS treatments.

Toshio Yamaguchi from Shin-yurigaoka General Hospital presented on MRgFUS ventro-oral (Vo) thalamotomy for focal hand dystonia. Previous research has demonstrated the efficacy of lesioning the Vo nucleus of the thalamus to alleviate the symptoms of focal hand dystonia such as writer's cramp and musician's dystonia. An initial pilot study (N=10) of unilateral Vo MRgFUS thalamotomy was performed. Motor features and adverse events were assessed by the functional neurosurgeon at baseline, 1 week, and 3 months after treatment. The target site was the Vo nucleus of the thalamus, which was 1 mm posterior to MC (middle AC-PC), 14 mm lateral from the midline and 2.5 mm above AC-PC line. All the patients were successfully treated with lesioning (average maximum temperature 60.1 degrees). Unusual task-specific finger movement improved immediately after the procedure in all 10 patients, which persisted for up to 3 months follow up. Although longer follow up is necessary to draw a definite conclusion, this pilot study suggests that MRgFUS Vo thalamotomy is safe, feasible, and effective for the treatment of focal hand dystonia.

Jorge Máñez-Miró from HM CINAC presented a case report of MRgFUS thalamotomy for multiple-sclerosis associated tremor. Up to 50% of multiple sclerosis patients present with tremor, which can be medically refractory. Both thalamic DBS and radiofrequency thalamotomy provide sustained benefit in selected patients. MRgFUS thalamotomy has been recently approved by FDA as a treatment for essential tremor and preliminary evidence suggests it could also improve tremor of other origins. MRgFUS reduces the risks related to surgery, and may be desirable for patients with multiple sclerosis. A 28-year-old female diagnosed with multiple sclerosis was referred for MRgFUS VIM thalamotomy to treat highly disabling right upper limb tremor refractory to medical treatment. Assessment was performed both at baseline and 3 and 6 months after treatment. Abolition of tremor was achieved and sustained at 6 months and 1 year. Mild facial asymmetry, moderate dysarthria and unsteadiness were present post-procedure; these resolved over time with a minimal dysarthria remaining at 1 year. Follow-up MRIs showed that the left thalamic lesion was greatly reduced in size. MRgFUS is a new therapeutic option for patients with multiple sclerosis, but the potentially slower recovery from side effects suggests that patients should be carefully selected and monitored during treatment.

Menashe Zaaroor from Technion-Israel Institute of Technology discussed a case series of successes and pitfalls with MRgFUS for patients with movement disorders. Seventy-one patients (72 procedures) including essential tremor, PD, and multiple-system atrophy underwent treatment. All patients underwent MRI and a battery of evaluations including CRST for essential tremor, and UPDRS in essential tremor, PD, and multiple-system atrophy, and quality of life. Seventy out of 71 patients were tremor free immediately after the procedure. Patients had improved tremor scores as well as improved quality of life. Fifty-one patients have follow-up data for between 6 and 42 months, with 78% of these patients experiencing sustained tremor relief. In all but two cases, the recurred tremor was significantly less disabling than before the procedure. When the tremor recurred, it was typically within the first six months after the procedure. To fine tune the target, the focal point was moved in steps of 0.1 to 0.5 mm according to the VIM somatotropic map. Some potential pitfalls include identifying and targeting specific tremor components, treatment of leg and head tremor, and setting patient expectations. Several further improvements are needed to improve MRgFUS such as shortening the treatment time, removing the need for head shaving, thermometry stabilization, improving intraoperative imaging, intraoperative physiological monitoring, and additional supportive studies.

Panel Discussion: Movement Disorders

Panel Moderators: M. Kaplitt and P. Fishman
Panelists: M. Burgess, M. Gallay, D. Gandhi, S. Guo, N. Young Jung, J. Máñez-Miró, T. Yamaguchi, and M. Zaroor

The panel discussed their opinions on the following topics:

1. **Given the convergence of radiological and electrophysiological methods for MRgFUS, what are some recommended pre-treatment imaging techniques?**

   Continued advances will improve image resolution. It's important to image the GPi as well as the interface with the internal capsule. Imaging the pyramidal tract is also important in order to avoid it during the procedure. The resolution of DTI needs to be further improved, as it is currently difficult to superimpose those images onto FGATIR or other types of images. There was a recommendation that if FGATIR is not being used, tractography should be superimposed on top of T2-weighted MRI sequences. This aids in target finding and fine tuning to reach the posterior GPi.

2. **Is there a good endpoint for assessment intra-procedure?**

   One participant mentioned that working in a team setting allows the neurologist to perform assessments during the procedure. Additionally, it's also important to monitor the optic tract, perhaps via evoked potential, because this is a major obstacle encountered when targeting the GPi.

3. **Is there an optimal endpoint assessment that can be done during, or shortly after, the procedure that indicates a durable lesion??**

   Traditional MRI is not useful because the lesion volume cannot be seen for 24 to 48 hours, and the final lesion volume may not be seen until one-year post-procedure due to the edema caused by the procedure. Diffusion-weighted MRI, as discussed during the session, might be useful to visualize cell death in the target location. 3D volumetric measurements in addition to an algorithm that can correct for the movement of the target over the course of treatment will help to determine the entire ablated volume during the procedure.

4. **When is it appropriate to perform a second procedure?**

   This depends on the patient. When the target was only partially ablated during the first procedure, it is useful to perform the second procedure as soon as possible. Reimbursement may provide an obstacle; if the payer is not willing to reimburse for the first procedure it is difficult to justify the second procedure.

Psychiatric Disorders

Presentations highlighted bilateral FUS capsulotomy for the treatment of treatment-refractory obsessive-compulsive disorder and major depression.

Jin Woo Chang from Yonsei University College of Medicine presented on bilateral thermal capsulotomy for MRgFUS for treatment-refractory obsessive-compulsive disorder (OCD) after 2 years of follow up. Eleven patients with treatment-refractory OCD underwent bilateral thermal lesioning of the anterior limb of the internal capsule (ALIC) using MRgFUS. Clinical outcomes were evaluated using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Clinical Global Impression (CGI) including improvement (CGI-I) and severity (CGI-S), Hamilton Rating Scale for Depression (HAM-D), and Hamilton Rating Scale for Anxiety (HAM-A) at 1 week and 1, 3, 6, 12, and 24 months following MRgFUS. Neuropsychological functioning, Global Assessment of Functioning (GAF), and adverse events were also assessed. After MRgFUS, Y-BOCS scores significantly decreased across the 24-month follow-up period. HAM-D and HAM-A scores also significantly decreased. GAF score significantly improved. There were no changes in cognitive function, except an improvement in memory after 2 years. Adverse events were mild and transient. In conclusion, the results suggest that bilateral thermal lesioning of the ALIC using MRgFUS may improve obsessive-compulsive, depressive, and anxiety symptoms in treatment-refractory OCD patients without serious adverse events. However, since this is an open-label, single-arm study, randomized controlled trials are needed to validate the results.

Jin Woo Chang from Yonsei University College of Medicine presented on bilateral thermal capsulotomy with MRgFUS for patients with treatment-resistant depression. Five patients received open-label bilateral thermal capsulotomy at the ALIC via MRgFUS in a proof-of-concept study and were followed for one year. However, in one patient, there was a failure to make a thermal lesion. Patients underwent comprehensive neuropsychological evaluations and imaging at baseline, 1 week, 1 month, 6 months and 12 months following treatment. Outcomes were measured with the HAM-D and Beck Depression Inventory, and treatment-related adverse events were evaluated. Three out of four patients showed almost immediate and sustained improvements in depression (a mean reduction of 61.1%). No adverse events (physical or neuropsychological) were reported in relation to the procedure. In addition, there were no significant differences found in the comprehensive neuropsychological test scores between the baseline and 6- or 12-month time points. This study demonstrates safety and efficacy of bilateral thermal MRgFUS capsulotomy in a small number of patients, but needs to be investigated in larger clinical trials. There are some technical challenges associated with MRgFUS including difficulty with energy delivery through the skull due to SDR, volume, thickness, incidence angle, and brain tissue properties.

Karim Mithani from Sunnybrook Health Sciences Centre at Toronto Weston Hospital presented on MRgFUS capsulotomy for OCD and major depressive disorder. Two prospective, single-arm, non-randomized, phase I, pilot trials of MRgFUS for non-invasively treating refractory OCD and major depressive disorder have been initiated with the goal of recruiting 10 patients with each diagnosis. MRgFUS will be used to create a ~5mm lesion bilaterally in the ALIC. Patients are being followed at 1 month, 3 months, 6 months, and 12 months post-operatively. Efficacy is being evaluated using various psychiatric scales such as the Y-BOCS and HAM-D. Preliminary data from three patients demonstrated that the Y-BOCS score was reduced in patients with OCD and the HAM-D was reduced in patients with major depressive disorder. Tractography with DTI showed that post-operatively the ALIC tracts were interrupted. Fractional anisotropy was used to look at white matter alignment, and preliminary evidence showed that it decreased after the procedure, but returns to baseline by 12 months. The clinical implications of this are unknown. In conclusion, MRgFUS is a potential treatment option for treatment-refractory OCD and major depression, and early results from a phase I trial suggest safety and efficacy.

Neurodegenerative Disorders

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

Nir Lipsman from Sunnybrook Research Institute presented on safety data from a phase I trial investigation FUS for BBB opening in Alzheimer's disease. Low-frequency MRgFUS in combination with intravenously injected microbubbles transiently opens the BBB, and reduces β-amyloid and tau pathology in animal models of AD. The safety and feasibility of MRgFUS to open the BBB within the right prefrontal cortex, on two occasions, in six patients with mild-to-moderate AD was investigated. Patients diagnosed with AD with Mini-Mental Status Exam score between 18 and 28 and [18F]-florbetaben PET positivity in the right frontal lobe were enrolled. Patients underwent two BBB opening procedures using the ExAblate 220 KHz system (InSightec), one month apart, and were followed for a total of three months. Primary outcome measures were safety, the number of adverse events, and feasibility, as determined by the leakage of gadolinium contrast on MRI due to increased BBB permeability. Secondary outcome measures were change in [18F]-florbetaben tracer uptake in the region of interest, and change in neuropsychological tests (e.g. ADAS-cog). In all patients, the BBB within the target volume was safely and repeatedly opened, with closure observed on follow-up MRI within 24 hours. Opening the BBB did not result in serious clinical or radiographic adverse events. There was no worsening of cognitive symptoms, and no changes in amyloid deposition. In conclusion, BBB opening for AD was safe and feasible; results from this study support the continued investigation of MRgFUS as a potential novel treatment and delivery strategy for patients with AD. The next step is a phase IIa study with repeated BBB opening targeted to the hippocampus and other regions of the brain that are positive for amyloid.

Gerhard Leinenga from the University of Queensland presented on the clearance of amyloid-β (Aβ) and tau pathology using scanning ultrasound (SUS) in preclinical AD models. AD is characterized by Aβ deposition contributing to extracellular plaques and tau deposition leading to intraneuronal tangles. Previous research demonstrated that SUS reduces amyloid plaque pathology. Next, the researchers aimed to determine the efficacy of SUS in aged APP23 mice that were treated with SUS four times over 8 weeks. Histology was analyzed four weeks after the last treatment. Amyloid was reduced by 58% as assessed by methoxy-XO4 fluorescence, and the proportion of large plaques was reduced. In addition, plaque-associated microglia were more numerous in SUS-treated mice. There was a significant correlation between plaque area and the number of microglia near plaques. A second study was completed in tau mutant K3 mice that develop early onset motor and memory impairment and have hyperphosphorylated and aggregated tau. Previous research showed that SUS could deliver anti-tau antibody fragments into the brain and reduce tau phosphorylation. Mice were treated weekly for 15 weeks, and SUS treatment improved motor function and memory impairment. Repeated SUS also reduced phosphorylated tau, and the underlying mechanisms are currently being investigated.

Christakis Damianou from Cyprus University of Technology discussed Aβ plaque reduction with antibodies crossing the BBB via FUS in a mouse model. The purpose of the study was to develop a positioning device for small animals and to use FUS BBB opening to remove Aβ plaques in the 5XFAD model of AD. A MRI-compatible positioning device was designed and a spherically shaped MRI-compatible FUS transducer was used (0.5 MHz, 5 cm diameter, focus at 10 cm) The treatment using FUS BBB opening showed reduction of amyloid plaques. In conclusion, this feasibility study demonstrated that by opening the BBB, it was possible to allow endogenous antibodies to enter the brain, thus eliminating Aβ plaques.

Nathan McDannold from Brigham and Women's Hospital presented results demonstrating that FUS-mediated BBB disruption improves anti-pyroglutamate-3 amyloid-β (pGlu3 Aβ) antibody effects in aged AD-like mice. pGlu3 Aβ is a pathological, highly neurotoxic form of Aβ found in deposits and water-soluble aggregates of human AD brain. Sixteen-month-old, male wildtype C57BL/6J and APPswe/PS1dE9 AD mice were used. Intravenous infusion of 500 µg murine anti-pyroGlu3 Aβ IgG2a mAb was administered immediately prior to FUS treatment. FUS was applied under anesthesia using an 835 kHz transducer (diameter 10 cm, focal length 8 cm) in conjunction with intravenous 100 µl/kg microbubbles. Burst sonications (10ms at 2 Hz) were applied for 100 s at two locations in each hemisphere in the hippocampus. Animals received three weekly treatments with behavioral testing 1 week after the last sonication. Amyloid burden, inflammation, and microhemorrhage were measured. Combination treatment showed a significant improvement in learning in the Water T-Maze test. FUS alone improved learning in wildtype mice and memory in AD mice in the contextual fear conditioning test. The combination treatment significantly lowered the Aβ42 and pGlu3- Aβ plaque load and increased synaptic markers in the hippocampus of AD mice. Plaque-associated microglia/macrophages were observed in AD mice with Aβ alone and combination treatment also induced monocyte/granulocyte/neutrophil infiltration and association with Aβ plaques. No changes in microhemorrhage were seen following FUS, antibody, or combination treatment. In conclusion, FUS may be a useful tool for facilitating the efficacy of anti-Aβ mAb immunotherapy presumably by increasing delivery to the brain, resulting in better Aβ clearance, synaptic protection, and hippocampal function. Interestingly, the combination treatment resulted in the presence of peripheral immune cells within plaques. Thus, this non-invasive method may have therapeutic potential when used in combination with mAbs for AD. treatment.

Qingxi Ma a student with Barbara Waszczak (Northeastern University) presented on the effects of FUS on delivery of intranasal glial cell line-derived neurotrophic factor (GDNF) DNA nanoparticles in the rat brain. GDNF is an endogenous neurotrophic factor that can protect and rescue dopaminergic neurons. Intranasal delivery of GDNF DNA nanoparticles bypasses the BBB to "transfect" cells in the brain, resulting in increased GDNF production within the brain. Previous work demonstrated a neuroprotective role for GDNF nanoparticles in a rat model of PD. FUS (270 kHz) with circulating microbubbles was applied to the forebrain and the midbrain after intranasal injection of GDNF DNA nanoparticles or saline. After 1 week, they observed whether microglia (Iba1 immunohistochemistry labeled with Alexa flour 488 dye) were recruited regardless of whether nanoparticles were delivered. Activated microglia were observed in clumps at sonication sites. In conclusion, the results showed that FUS enhances the transfection of brain cells after intranasal delivery of GDNF DNA nanoparticles.

Barbara Waszczak from Northeastern University further discussed the project described in Qinxi Ma's presentation on the effects of FUS on delivery of intranasal GDNF DNA nanoparticles in the rat brain. ELISA was used to measure expression levels of GDNF at sonication sites and immunohisto-chemistry (IHC) was used to examine regional and cellular transfection patterns. FUS with circulating microbubbles significantly increased GDNF expression in the sonicated hemisphere. FUS caused transfection of cells that were not consistently perivascular in location, and were neither neurons nor astrocytes. Most of these cells expressed the microglial marker Iba1. In conclusion, these results demonstrate that FUS with circulating microbubbles enhances transfection and transgene expression after intranasal administration of DNA nanoparticles, and that the transfected cells at sonication sites are predominantly microglia.

Mike Bobola from the University of Washington presented on accelerated remyelination with transcranial and pulsed FUS (pFUS) in a mouse model of MS. MS impacts approximately 400,000 in the United States and is the leading cause of disability among young to middle aged people in the developed world. The hallmark of this disease is demyelination that prevents neuronal communication. The researchers investigated whether FUS stimulation of MS lesions in a mouse model (cuprizone) could reduce demyelination or accelerate remyelination (N=11). Using subdermal EEG, pFUS (pFUS) protocols

capable of activating the brain were developed. Histological analysis showed that FUS significantly accelerated remyelination at the site of sonication. The next steps are to perform more histology, analyze MRI, add electron microscopy, change to an auto-immune mouse model, and optimize FUS protocols.

Blood-Brain Barrier Opening

Presentations highlighted preclinical research using FUS plus microbubbles to induce BBB opening as a mechanism to enhance delivery of potential therapeutics. Additionally, preliminary clinical studies for BBB opening were presented.

Tali Ilovitsh from Stanford University discussed characterizing microbubble agent oscillation following 250 kHz insonation for BBB opening. This research characterized microbubble oscillations at a frequency of 250 kHz and compared with 1 MHz. Ultra-high-speed optical imaging, operating at 100 Mfps recorded the oscillations of single microbubbles following a short ultrasound pulse with a center frequency of 250 kHz. As compared with the 1 MHz center frequency, microbubble expansion was enhanced for the 250 kHz transmission. Passive cavitation detection also demonstrated an enhanced effect of 250 kHz compared with 1MHz. The range of peak-negative pressure yielding stable cavitation is narrow for the 250 kHz transmission frequency (75-190 kPa for a microbubble with a radius of 0.75 µm) as compared to the higher frequency (245-500 kPa for the same microbubble radius). In mice experiments at a pressure of 75 kPa, no BBB opening was observed. For pressures of 100 and 150 kPa, safe BBB opening was observed; however, at pressures above 190 kPa (e.g. 190 and 250 kPa), inertial cavitation resulted in hemorrhage. Microbubble oscillations at a center frequency of 250 kHz are enhanced compared to higher frequencies in the MHz range. Due to the high nonlinear expansion of microbubbles at a center frequency of 250 kHz, the development of safe and successful protocols for therapeutic delivery to the brain utilizing a similar center frequency requires consideration of the narrow pressure window between stable and inertial cavitation.

Jürgen Götz from the University of Queensland presented on feasibility studies in mice and sheep to validate ultrasound-mediated BBB opening. Previous work has demonstrated scanning ultrasound combined with microbubbles can improve memory and remove toxic protein aggregates in an AD mouse model. In order to develop scanning ultrasound into a treatment modality for human patients the technology needs to be assessed in larger animals, and long-term safety needs to be established. In mouse studies spatial memory and neuronal morphology were not adversely affected nor was long-term potentiation as a cellular correlate of memory. In a stepwise manner, 12 sheep were used to establish a sonication protocol using a spherically focused transducer. Successful opening of BBB in sheep was demonstrated. Current research is underway with a custom-made probe under MRI guidance in a multiple recovery paradigm in sheep

Francesco Prada from the Focused Ultrasound Foundation presented on the use of intraoperative contrast-enhanced ultrasound for microbubble visualization. Contrast-enhanced ultrasound was used to visualize brain tumors. Microbubble distribution in the brain according to time intensity curves during FUS is unknown. Qualitative analysis suggested that the intensity of enhancement of microbubbles at peak phase and the timing of distribution was different in glioblastoma compared with low-grade glioma. A retrospective analysis (N=102) was performed. Microbubble distribution was uneven within brain tumors. In normal brain, microbubble concentrations changed with different vascular phases (arterial parenchymal and venous) and showed different concentrations according to vessel density (gray/white matter). Contrast-enhanced ultrasound provides information about microbubble distribution in time and space with time intensity curves. Additionally, fusion imaging, combining contrast-enhanced ultrasound imaging with MRI, could help visualize glioblastoma for surgical guidance for FUS treatments.

Bingbing Cheng from the University of Texas Southwestern Medical Center discussed the influence of nanobubble concentration on BBB opening using FUS and acoustic feedback control. A portable ultrasound system combined with a stereotactic platform and brain atlas was developed to target brain regions without MRI. This system has recently been combined with a hydrophone to monitor acoustic emissions during BBB opening. Different kinds of microbubbles were compared (commercial and custom made), but the harmonic emission and acoustic control were more consistent with a custom-made nanobubble (200-300 nm). The custom nanobubble is similar to other gas bubbles, with a lipid shell; however, the concentration is higher (2.9 ± 0.3 x 1011 mL). The data suggested nanobubbles have an in vitro persistence of ~10, 5, and 1 minutes and in vivo circulation time of ~10, 5, and 6 mins at concentrations of 1:1, 1:10, and 1:100, respectively. A feedback control algorithm was implemented, and in vivo studies were performed in a rat model to evaluate acoustic emissions and BBB opening at different nanobubble concentrations and AUC response increased with the pressure as expected. Successful maintenance of the AUC at a target level was achieved with different microbubble concentrations. Histological characterization did not show damage to the neuron or parenchyma. The next step is to determine treatment duration, evaluate tissue response under different conditions, and drug delivery efficiency under different conditions.

Arthur Lung from NaviFUS presented on the NaviFUS device for clinical transcranial brain applications. NaviFUS was established in 2015 to develop a FUS device capable of steering and targeting specific brain regions and to be able to sonicate a large treatment volume. The NaviFUS device uses an optical tracking system with a neuronavigational guidance that does not need MRI for BBB opening. The device also uses software in combination with an ultrasound phased array for high-speed targeting of large volumes to shorten the procedure. A feasibility study (N=6) was completed to evaluate the safety of transient BBB disruption and to find the tolerated ultrasound dose of transient opening of the BBB in patients with recurrent glioblastoma (GBM). FUS was performed 7 to 10 days prior to tumor debulking. BBB opening was confirmed with DCE MRI. Two patients were treated with the device with confirmed BBB opening that closed within 24 hours post-treatment. Additional patients will be treated in the pilot study.

Mark Burgess discussed transcranial imaging of acoustic cavitation. MRI is good for targeting and confirmation of BBB opening, but is not useful for intraoperative monitoring, and neuronavigational FUS is good for targeting but lacks the ability to confirm BBB opening and intraoperative monitoring. A custom-made FUS system was used in the experiments, and consisted of an imaging array (1.5 MHz), a FUS transducer (0.5 MHz) coupled with power cavitation imaging that acquires stacks of images and corrects for motion. Transcranial passive cavitation imaging was performed in non-human primates. A bolus injection of Definity microbubbles was intravenously injected at five times the clinical dose (50 L/kg) during imaging. The hippocampal region was targeted using the neuronavigation system. Image sets were acquired at ultrafast frame rates (>1000 frames per second) for calculation of mean intensity images, i.e. power cavitation images. Spatiotemporal clutter filtering based on singular value decomposition was used to increase power cavitation image contrast over a range of FUS peak-negative pressures (0.1 – 0.9 MPa). Power cavitation images were registered with pre-acquired MRI images to identify the spatial distribution of acoustic cavitation in the underlying vasculature. This technique allowed for power cavitation image intensity over time (i.e. cavitation dose). Future work will look at whether power cavitation images can predict the location of BBB opening.

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Epilepsy, Stroke, Neuropathic Pain

Presentations highlighted the plan for a first-in-human trial of FUS thalamotomy for epilepsy and preclinical work regarding BBB opening in combination with neurotoxin for epilepsy. Results for several different FUS techniques (thermal ablation, microbubbles combined with neurotoxin, and neuromodulation) for the treatment of pain in preliminary clinical trials were also described. Additionally, FUS with microbubbles and BBB opening for the delivery of therapeutics for acute ischemic stroke was also presented.

Vibhor Krishna from the University of Maryland presented the plan for a pilot study of thalamotomy for the prevention of secondary generalization in epilepsy. Patients with temporal lobe epilepsy that do not want surgical dissection are good candidates for FUS. Evidence for thalamotomy of the anterior nucleus of the thalamus comes from DBS. Patients with DBS in this brain region had seizure reduction even without stimulation from the DBS device. Technical safety studies in brain phantoms demonstrated safety and feasibility of the target. Patients will be enrolled if they have medically-refractory epilepsy, focal onset seizures with or without generalizations, with ≥ 4 seizures per month. The ventral portion of the anterior nucleus (AN) will be the target, based on DBS data. Safety will be assessed by the absence of side effects, defined as new-onset neurological deficits or performance deterioration on neuropsychological testing. Feasibility is defined as the ability to create a lesion within the AN. Secondary outcomes will include changes in seizure frequency and patient reported quality of life measures. Imaging analyses will be performed to study changes in functional connectivity, as well as in structural and microstructural brain anatomy. In conclusion, this will be the first known clinical trial to assess the safety and feasibility of FUS ablation of the AN in patients with treatment-refractory partial-onset epilepsy.

Kevin Lee from the University of Virginia discussed non-invasive neuronal lesions sparing non-targeted cellular structures for medically-refractory epilepsy. Resection or ablation of brain tissue can be quite effective for treating medically-refractory epilepsy. However, existing surgical procedures possess considerable limitations and potential complications. Resective surgery can be highly invasive, resulting in bleeding, infection, blood clots, strokes, seizures, swelling of the brain, and off-target damage. Development of a treatment paradigm for epilepsy using MRgFUS combined with microbubbles and BBB opening is under investigation. A neurotoxin would be co-administered in order to destroy neurons, while sparing non-neuronal tissue, in a targeted area. Several brain regions have been targeted in the rodent brain (neocortex, hippocampus, thalamus, striatum, etc.), and each area exhibited degenerating neurons. Axons and ventricular wall were spared in the targeted area. This technique could be useful to disconnect dysfunctional brain circuitry in a precise, conformal, and non-invasive fashion, and it may also be applicable in other brain disorders with dysfunctional brain circuitry.

Shayan Moosa from the University of Virginia discussed the plan for a clinical trial of FUS medial thalamotomy for the treatment of trigeminal neuropathic pain. Chronic pain, and neuropathic pain, is very difficult to treat. Stereotactic treatment has evolved to treat the medial pain system. Historically, medial thalamotomy, the termination of the primary pain pathway from the spinal cord, has suggested efficacy for the treatment of various types of pain. This study is rigorously designed as a randomized, sham-controlled, double-blind trial (N=10). FUS lesioning of the bilateral medial thalamus in patients with severe, treatment-refractory, chronic trigeminal nerve pain will be performed. Validated pain scales and neuropathy-specific scales will be utilized by a multi-disciplinary team of experts in the fields of FUS, pain, and peripheral neuropathy. Functional brain imaging will determine objective measures of treatment effect.

Ronen Cozacov from the Rambam Health Care Campus presented on the treatment of neuropathic pain in amputated patients using MRgFUS technology. Neuroma is a non-neoplastic lesion that develops following nerve injury, due to trauma or surgical procedures (e.g., amputation) and can result in neuropathic pain. Current treatment methods include pain control using analgesics, the re-approximation of nerve endings in the injury site and re-embedding of the nerve stump away from scar tissue.

Results from a feasibility study in five patients with neuropathic pain treated with MRgFUS were presented. Results are still preliminary, and show the ability to target and ablate neuroma using FUS. Several factors seem to contribute to ablation of the neuroma, including usage of high energy sonications, hypo-intensity of the neuroma on T2-weighted images, location of bone tissue in the far field and adjacent to the neuroma, and homogeneity of tissue in the near-field of the neuroma. Initial results also suggest that partial ablation of the neuroma might also reduce pain. In conclusion, the initial clinical experience with MRgFUS for treatment of neuropathic pain in patients with amputation, shows a high safety profile and suggests that this non-invasive procedure is a feasible treatment modality. Additional clinical experience is required to fully evaluate the limitations of this novel treatment approach, as well as to optimize patient selection and treatment methods for improved clinical outcome.

Mike Bobola from the University of Washington presented on intense FUS stimulation of intact versus transected peripheral nerves. This study aimed to determine if transected nerves and nerves after amputation are more or less sensitive to intense FUS stimulation relative to intact nerves. FUS was applied to two groups: one group of standard amputees with transected nerves and healthy volunteers. As controls, they stimulated ipsilateral muscle, contralateral, intact nerves in the amputation cohort, and intact nerves in healthy volunteers. Intact nerves across all cohorts had comparable sensitivity to FUS stimulation. There was greater sensitivity to FUS in transected nerves in standard and targeted muscle reinnervation (TMR) amputees, and patients with neuropathic TMR had greater sensitivity than non-neuropathic TMR.

Hermes Kamimura from Columbia University discussed temperature and cavitation monitoring for FUS peripheral neuromodulation. Previous research has demonstrated that FUS can modulate the central and peripheral nervous systems (PNS). Electric stimulation of the PNS can also inhibit hyperactive motor reflexes observed in spinal cord injuries, MS, and movement disorders such as cerebral palsy. The development of a clinical-FUS PNS system allows for the investigation of acoustic radiation force (ARF) as the primary mechanism (by avoiding cavitation and temperature increase) of peripheral nerve stimulation with FUS. Sonications were performed at 3.1 MHz (Sonic Concepts) in male C57BL/6 mice in vivo and ex vivo chicken breast samples with average pressure attenuation of 3.5 dB/cm@1 MHz (similar to human muscle). Sonications were performed with pulse durations varying within 32-1000 μs and peak-negative pressure (PNP) levels from 3 to 11 MPa. In mice and humans, safe activation of the median nerve was indicated by variable sensations for low mechanical index (no cavitation) and no temperature effects. Temperature was controlled by keeping pulses short. Future experiments will attempt to improve targeting with tissue displacement imaging and maximize the clinical set up (minimize MI while avoiding cavitation).

Pedro Norat from the University of Virginia discussed FUS with intra-arterial mitochondria transplantation for ischemic stroke. Mitochondria are critical to cell survival, and transfer from astrocytes to neurons after stroke. FUS was used to selectively open the BBB at the site of stroke induced injury to enable delivery of therapeutics, mitochondria isolated from muscle, to assist with minimizing reperfusion injury in the ischemic penumbra after stroke. Cerebral ischemia was modeled in mice by performing selective middle cerebral artery occlusion for 1 hour followed by reperfusion. Six hours after reperfusion, mice were treated with microbubbles and FUS to open the BBB followed by intra-arterial delivery of mitochondria. As expected, stroke induced partial opening of the BBB at the site of ischemia. FUS allowed for a more robust opening of the BBB and enhanced the intra-arterial delivery of mitochondria to the ischemic penumbra. Further work will investigate whether the delivery of mitochondria make a difference in neuronal survival and whether mitochondria are necessary to neuronal survival in the stroke area.

Catherine Gorick from the University of Virginia presented on FUS-mediated transfection of cerebral vasculature without detectable BBB opening. Gene therapy approaches to revascularization after stroke could benefit from endothelial cell-selective transfection, which could permit modulation of the vasculature without affecting the BBB. Pulsed sonications at lower pressures (1 MHz, 19 ms pulses, 0.5 Hz pulse

repetition frequency (PRF)) with microbubbles were used for activation and sonoporation of endothelial cell membranes without opening the tight junctions. The BBB was maintained at 0.1 MPa. Cationic lipid shelled MBs (1-3 microns) were electrostatically coupled with reporter gene-bearing plasmid DNA (luciferase or mCherry) and injected intravenously. Transfection was assessed by bioluminescence or immunofluorescence. At increasing pressures, there was significantly more transfection of extravascular cells. RNA-seq demonstrated that microbubble activation with low pressure FUS does not upregulate inflammatory pathways 24 hours post-treatment. Cavitation doses are correlated with PNP and predict associated BBB opening. In conclusion, acoustic emissions thresholds can be used to distinguish between BBB opening and BBB-maintaining regimes.

Neuromodulation

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

Jerome Sallet from the University of Oxford presented on cortical transcranial ultrasound stimulation. Offline transcranial ultrasound stimulation in non-human primates followed by fMRI in an ultrasound-free environment was performed. A single-element ultrasound transducer was operated at 250 kHz with 30 ms bursts of ultrasound with a pulse repetition rate of 10 Hz. The total duration of the stimulation was 40 s, with a peak-to-peak voltage of 130 V, corresponding to a PNP of 1.2 MPa. Sonication was performed off line and whole-brain BOLD fMRI data were collected in a 3 T MRI scanner with a full-size horizontal bore from each animal at least 20 minutes after sonication. FUS was used to stimulate the perigenual anterior cingulate cortex (ACC). Functional connectivity analysis was performed, and 40 s stimulation resulted in disruption of functional connectivity. Sonication of the perigenual ACC resulted in disruption of the normal functioning of the medial premotor cortex as well.

Morteza Mohammadjavadi from Stanford University discussed how the elimination of auditory pathway activation can affect motor responses. The researchers investigated whether mice could hear commonly used ultrasound stimuli, whether unintentional off-target auditory system activation could be eliminated, whether motor responses were evoked by ultrasound due to indirect activation of the auditory system, and whether this response was due to activation of any peripheral systems. The US stimuli were pulsed waves with 1.5 kHz PRF, pulsed wave (1.5kHz) with 8 kHz PRF, PW (8kHz), continuous wave with rectangular envelope, or continuous wave with smoothed envelope. US parameters, except the continuous wave with smoothed envelope, caused an auditory brain response suggesting that the mice could hear the US stimuli. Smoothing the waveforms eliminates the auditory response without affecting the motor response. US-evoked motor responses are not due to activation of the auditory system and are not consistent with a startle-like response.

Pooja Gaur from Stanford University presented a histological study of FUS neuromodulation and MR-ARFI in sheep to evaluate safety. Anesthetized male Dorset cross sheep underwent transcranial focused ultrasound (N=5), repeated FUS (N=3), or a sham procedure (N=2). MR-ARFI (550 kHz transducer) was applied to subcortical locations with acoustic power between 130 and 200 W. Neuromodulation was also performed at acoustic powers between 8.5 and 34 W with a range of pulses and target locations. There were no histological findings observed at sites of FUS targeting. Red blood cells were found in the meninges, and some bone fragments were found in all groups. There was no evidence of concurrent histologic lesions (i.e. listed above) in regions of red cell extravasation. There was one case of neuronal necrosis observed near the skull boundary, likely due to bone heating from consecutive experimental trials. The absence of concurrent histologic lesions suggests that areas of extravascular red blood cells seen across both hemispheres and experimental groups were artifacts due to post-mortem tissue extraction. However, these findings suggest that it is important to model the potential for skull heating from FUS.

Wonhye Lee from Brigham and Women's Hospital discussed transcranial FUS-mediated motor cortical stimulation in awake rats. Anesthesia is known to affect overall responsiveness to sonication, and more research on awake small animals is needed to better understand the efficacy of FUS brain stimulations. The researchers developed a 3D-printed wearable headgear system with a miniature single-element FUS transducer. Three groups were tested: light anesthesia using ketamine/xylazine, isoflurane anesthesia, and awake rats. The wearable headgear stimulated the brain and elicited responses from rats including various motor responses. In comparison to anesthetic conditions, awake rats showed smaller range of movement, lower threshold intensity, higher response rates with decreased variability, and an increased portion (>30%) or responses having short latency (<30 ms). Animal behavior and post-mortem histology suggested safety of repeated, long-term use of FUS brain stimulation.

Colleen Curley from the University of Virginia presented on FUS tissue modulation with augmented nanoparticles in the brain. Previous research demonstrated that PEGylated brain-penetrating nanoparticles (BPN) could cross the BBB to the central nervous system (CNS) with FUS. The objectives were to determine whether pre-treating brain tissue with pFUS may be used to enhance BPN dispersion in the CNS via activation of mechanosensitive transient receptor potential ankyrin 1 (TrpA1) and/or vanilloid (TrpV1) calcium channels and augment BPN-mediated transfection following trans-BBB delivery of BPN. FUS pre-treatment increased the volume of transfected brain tissue (1.8- and 2.5-fold in C57Bl6 mice and Sprague-Dawley rats, respectively) after convection-enhanced delivery of gene-vector BPN. This effect was abolished in TrpA1-/- mice, but not in TrpV1-/- mice, thereby identifying TrpA1 as a key biological mediator of FUS-enhanced penetration. In a clinically-operable treatment paradigm guided entirely by MR imaging, we demonstrated that pre-conditioning brain tissue with pFUS before opening the BBB elicits multi-fold enhancements in subsequent transgene expression, without significant tissue heating or overt signs of gliosis. FUS pre-conditioning did not affect the magnitude or duration of BBB opening nor temperature.

Pierre Pouget from Institut Langevin presented on the modulation of visual evoked response by non-invasive GABA. The feasibility of local, non-invasive delivery of an inhibitory neurotransmitter (GABA) to modulate the visual cortex activity of non-human primates was investigated. The BBB was opened in the visual cortex of two macaques using a single-element FUS transducer at 245 kHz and microbubbles. Control runs (baseline, after ultrasound alone, and after ultrasound + microbubbles) were performed before GABA was injected intravenously (0.1 to 6 mg/kg) and the 'GABA' runs were conducted. Electrophysiological data were filtered and averaged. The decrease of the visual evoked potentials amplitudes as the difference between the maximum and the minimum P1 peaks over the five first GABA runs were calculated for each session. P1 amplitude increased linearly as the GABA dose increased. Results showed that the influence of FUS with microbubbles got stronger as time increased after visual stimulus onset, compared to GABA-induced effects. GABA accounts for 90% of the effects during the first 100 ms, 42% during the 100 to 200 ms period and 50% during the 200 to 300 ms period. In conclusion, the modulatory impact of the local delivery of GABA in the brain is at maximum (90%) within the first 100 ms after visual stimulus onset.

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Tuesday October 23, 2018

Brain *continued*

Brain – Technical

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

Xue Feng from the University of Virginia discussed accelerated real-time 3D MR thermometry using a retraced spiral-in/out trajectory. Real-time MR thermometry, usually based on the proton-resonance frequency shift, is a key aspect of MR-guided focused ultrasound procedures. The purpose of this study was to develop accelerated real-time 3D MR thermometry using a retraced spiral-in/out (RIO) trajectory with Kalman filter reconstruction. A 3D RIO thermometry sequence based on stack-of-spirals was implemented on the RTHawk platform to enable real-time sequence control and monitoring of a FUS sonication. A fully sampled spiral k-space trajectory was designed with 24 interleaves and 12 slice-encoding steps. Temperature maps at peak temperature frame for all 12 slices were obtained and the temperature rise could be seen in three slices (9 mm). A retrospective under-sampling experiment showed reconstruction accuracy. Real-time 3D thermometry, using RIO trajectory with acceleration along slice encoding, can achieve high spatial and temporal resolution. The accuracy of reconstruction using a Kalman filter was improved. This method will be further validated with preclinical and clinical experiments.

Costas Arvanitis from the Georgia Institute of Technology and Emory University presented on closed-loop control of cavitation activity using passive acoustic mapping. The objectives of this study were to develop methods for controlling microbubble oscillation. Stable cavitation correlates with safe and reversible BBB opening, but inertial cavitation is associated with tissue damage. The pressure separation between these two events is very small. Acoustic emissions can be used to control the microbubble oscillation. A passive acoustic mapping-based controller was developed as a closed-loop controller that calculates acoustic emissions using the angular spectrum. This method has fast reconstruction time and is frequency selective. The excitation level is calculated, and the controller can increase or decrease the pressure based on the acoustic emission threshold. Phantom experiments showed that the passive acoustic mapping controller had spatiotemporal control of microbubble oscillations. Future work will test the controller in vivo during FUS BBB opening.

Zaiyang Long from the Mayo Clinic discussed the effect of CT exam protocols on SDR calculations performed during MRgFUS treatment planning. MRgFUS of the brain requires a head CT scan to assess SDR. Treatment on the Insightec ExAblate Neuro system requires CT images using a defined scan protocol and reconstructed with a specific reconstruction kernel, which is not available on all scanner platforms. It is unclear how other kernels or alternate exam protocols affect SDR calculations. The objective of this study was to compare SDR from different scan protocols and reconstruction kernels. A fixed head specimen was scanned on both Flash and Force scanners using the current clinical protocol under institutional review board (IRB) approval. Other variations in exam protocols were also tested, including different mAs, slice thickness, smoother kernels such as H30 and Hr38, and various head positions relative to the scanner (up to 50 degrees lateral rotation or tilting superiorly or inferiorly using the standard head holder). In addition, raw data of a patient's head exams on the two scanners were obtained and used to reconstruct anonymized H60 and Hr69 images. Images were exported to the treatment system where SDR scores were computed. SDR scores obtained using the H60 kernel on the Flash were identical to those obtained using Hr59 on the Force. On both platforms, using smoother kernels led to higher SDR scores, relative to H60 or Hr59. While thinner slice and increment did not cause changes, using a thicker slice of 2 mm resulted in increased SDR scores. Changing the relative position of the head resulted in a 5% difference in SDR scores. Increasing or decreasing radiation

resulted in consistent SDR scores (0.40) on the Force, and SDR scores of (0.38-0.39) on the Flash. Patient images demonstrated SDR of 0.47 on the Flash and 0.48 on the Force. In conclusion, Hr59 kernel on the Force scanner resulted in similar SDR scores as the recommended H60 kernel on the Flash scanner based on specimen and clinical images. Smoother kernels and thicker slice thickness caused SDR score differences higher than published standard deviation of SDR score measurement, and should be avoided. On the other hand, changing head positioning or radiation dose resulted in minimal differences, and were acceptable. These results suggest that patient head positioning does not have to be stringently restricted and there is potential to reduce radiation dose.

Henrik Odéen from the University of Utah discussed the evaluation and tradeoffs of 2D and 3D Cartesian magnetic resonance temperature imaging (MRTI) for brain applications. Magnetic resonance temperature (MRT) measurements for FUS brain applications ideally need to have high enough spatial and temporal resolution (on the order of 1x1x3 mm and 3-5 s) to accurately monitor the fast temperature changes occurring during FUS. High precision currently leads to a long scan time. Current procedures utilize a single 2D GRE single slice and single echo. A proposed solution is to use multi-echo or a planar imaging approach. MRT was carried out on a 3T scanner, with measurements taken over 60 s. The multi-echo sequence had a smaller off-resonance shift. Echo-planar imaging was able to obtain larger coverage (7 slices) in the same scan time with smaller off-resonance shifts, but there was some 'ghosting' in the images and lower precision. In conclusion, 3D MRTI can detect focal spot shifts, but this results in lower precision and a longer scan time.

Jonathan Sukovich from the University of Michigan presented on real-time transcranial histotripsy monitoring and localization. Histotripsy is a cavitation-based ultrasound therapy which is under investigation for transcranial applications, with demonstrated rapid and accurate lesion generation through the skull. The objective of this study was to evaluate the use of acoustic cavitation emission (ACE) signals to monitor and localize cavitation activity in real time during transcranial histotripsy treatments, and to use the same transducer for both treatment and detection. Histotripsy pulses were delivered through three excised human skullcaps using a 256-element, 500 kHz, hemispherical histotripsy transducer with transmit-receive capable elements. Treatment monitoring and localization was accomplished by back-projecting the acquired ACE signals into the field to form signal intensity maps of the transducer's focal volume. Pulses were electronically steered through a 1 cm diameter spherical volume centered at the geometric focus of the array through the skullcaps at PRF's of 1 Hz, 30 Hz, and 100 Hz to generate cavitation. There was good agreement between the locations of the bubbles found by back-projecting ACE signals into the field, hydrophone measurements, and 3D imaging. Precision error increased with PRF, but remained bounded to within the size of the bubbles. In conclusion, the feasibility of using ACE signals to monitor transcranial histotripsy therapies in real time was demonstrated.

Sumeeth Jonathan from Vanderbilt University discussed targeting FUS neuromodulation with optical tracking-guided MR-ARFI. MR-ARFI pulse sequences enable localization and targeting during FUS thermal therapy, but there are no developed tools for FUS neuromodulation target localization. Optical tracking MR-ARFI pulse sequences for MRgFUS neuromodulation are under development. MR-ARFI uses motion-encoding gradients synchronized with FUS to visualize the tissue displacement caused by radiation force. Displacement images were acquired using a diffusion-weighted spin echo 2D MR-ARFI pulse sequence implemented on a high-field 7.0 T scanner. Sonications were performed at 802 kHz with a low duty cycle (2.9 MPa free-field PNP/3.1 mechanical index) using an MRI-compatible FUS transducer. The encoding duration was 3.0 ms, similar to the FUS duration. Optical tracking enables real-time 3D position tracking of the transducer for in vivo targeting. Optical tracking maximizes MR-ARFI derived displacement sensitivity ex vivo. In conclusion, the proposed optical tracking workflow was used to guide MR-ARFI to produce acoustic beam maps for targeting ultrasonic neuromodulation in vivo. Ongoing studies will demonstrate the effectiveness of FUS in modulating the function of relevant neural circuits in non-human primates.

Steve Leung from Stanford University presented on the effect of acoustic parameter sets on transcranial FUS simulations. In transcranial FUS applications, the heterogeneity of the patient's skull alters the focal spot (position, temperature, and shape). 3D numeric simulations can be used to predict these focal spot characteristics and make corrections. For every voxel in a skull model, acoustic properties can be assigned according to its CT Hounsfield unit (HU) value. However, in the literature, there is substantial variability in the acoustic properties used for transcranial FUS simulations. The purpose of this study was to investigate how a specific set of simulations can be affected by different published values for acoustic properties. Patient specific skull models were derived from CT images, which were acquired on a General Electric scanner with 120 kVp, medium filter, and BONEPLUS reconstruction kernel. Every voxel was assigned acoustic properties according to its CT HU value. The hybrid angular spectrum method was used for simulations. MR-thermometry data were acquired during FUS treatment of patients with essential tremor, in which the ventral intermediate nucleus of the thalamus was the primary target. We compared the MR thermometry and simulation focal spots to evaluate simulation accuracy. Simulated positions were not affected, but simulated temperature was greatly affected. The study-dependent acoustic properties resulted in a large range of simulated temperatures. In conclusion, there is substantial variability in the acoustic properties used for transcranial FUS simulation. However, this study did not determine optimal acoustic parameters.

Sumeeth Jonathan from Vanderbilt University presented an update on the volumetric thermometry challenge to expand the transcranial treatment envelope. Current temperature imaging is done with 2D single slice, which works well in midbrain targets. However, targets that are closer to the skull are at a greater risk for skull heating. To ensure safety, temperature mapping of the whole brain is ideal. Several groups have proposed new imaging pulse sequences and reconstructions to meet this need, but each were implemented on different scanner platforms (GE, Siemens, and Philips) and with different FUS systems, and a careful comparison between approaches has not been completed. The objective of this study was to compare the different sequences on the same scanner and FUS platform. Sequences tested include 3D segmented echo-planar (EPI), RIO stack-of-spirals, and EPI stack-of-stars. Volume coverage, frame rate, and temperature precision tradeoffs were compared. To date, all three sequences have been implemented in RTHawk. Distortion occurred with the addition of the water bath. More work is necessary to improve image quality in the presence of the water bath. Optimal volume coverage versus scan time tradeoff is currently being evaluated. In vivo and heating scans will be repeated along with several improvements. All three original temperature reconstructions will be compared.

Jean-François Aubry from Institute Langevin presented on low-cost transcranial FUS to push the limits of single-element technology. A single passive cavitation detector (PCD) can discriminate between cavitation in the water bath or inside the brain and a single focused transducer can be used to achieve transcranial focusing. Cavitation inside or outside the skull has different frequencies because of the filtering effect of the skull. Therefore, a threshold level of cavitation can be used to filter signals inside the skull. Transcranial focusing can be done with a single element. The acoustic lens can be cast in silicone with a 3D-printed mold. Then, the quality of the focusing through the skull is assessed by performing a 3D scan of the pressure field. Focusing can be done by moving both the lens and the transducer. In conclusion, a single element covered with a patient specific acoustic lens can restore focusing though the skull. Furthermore, safety can be improved by binary localization of cavitation activity with one single PCD.

Kamyar Firouzi from Stanford University presented on efficient transcranial ultrasound delivery via excitation of Lamb waves. The development of the next generation of transcranial devices should aim to reduce costs without compromising efficiency or safety. Current methods rely on normal incidence, which leads to excess skull heating and has a limited treatment envelope. Lamb waves are multi-modal and dispersive guided elastic waves propagating in bounded structures (waveguides), and efficiently leak into surrounding medium. A wedge-shaped transducer can utilize guided Lamb waves in the skull as an efficient way of transmitting the ultrasound beam into the brain. Transmission efficiency is by virtue of a double-mode-conversion mechanism, one from the wedge into selective Lamb waves in the skull and

the other from Lamb waves into the brain. Benefits include the ability to selectively excite Lamb waves, improve transmission efficiency, and eliminate standing waves thereby reducing skull heating. The main constituents of the transducer array are wedge transducer elements arranged over a wedge ring to provide a focusing mechanism. The array was validated in simulation experiments. The next step will be to conduct experiments with human skull fragments. In conclusion, the preliminary results demonstrate the validity of the approach both for mode-conversion and for overcoming attenuation.

Oncology

Sessions on this day highlighted technical, preclinical, and clinical results demonstrating the potential of FUS for treatment of cancer (brain tumors, immunotherapy, liver, pancreas, kidney, and bone).

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 chemotherapeutics are ongoing. Preclinical results demonstrated several methods by which FUS could treat brain tumors: BBB opening, mechanical ablation, and sonodynamic therapy.

Jin Woo Chang from Yonsei University College of Medicine discussed BBB opening in patients with GBM undergoing standard chemotherapy (temozolomide). This study assessed the safety and feasibility of BBB opening combined with temozolomide in patients with GBM following tumor debulking surgery. BBB opening with microbubbles was performed on the first day of chemotherapy treatment during the treatment phase (6 weeks) and maintenance phase (one week per month for 6 months) in the region of the tumor. Two patients have already begun treatment. Contrast-enhanced MRI images confirmed BBB opening. There were no signs of hemorrhage in the two patients treated so far. Side effects appear to be related to temozolomide and not BBB opening. Preclinical work on efficacy and safety of BBB opening in rats and mice has already been completed.

Alexandre Carpentier from Assistance Publique Hospitaux De Paris presented on BBB opening with an implantable low-intensity pulsed ultrasound (LIPU) device. In a preliminary, first-in-human trial, patients with GBM were implanted with one or three 1 MHz, 10-mm diameter cranial devices (SonoCloud®) in burr holes during debulking surgery or during a dedicated procedure under local anesthesia. Ultrasound dose was escalated over 7 patients (0.4-1.15 MPa). The implantable ultrasound device was activated monthly via a transdermal needle during a 15-minute procedure to transiently open the BBB before intravenous administration of carboplatin. BBB opening was visualized using post-sonication T1 weighted contrast-enhanced MRI. Device or procedure-related adverse events were transient and manageable and included edema and facial palsy. No carboplatin-related neurotoxicity was observed. Patients with no, or poor, BBB opening (n=8) had a shorter median progression-free survival and overall survival than patients with clear BBB opening (n=11). In conclusion, LIPU was well tolerated and may increase the effectiveness of drug therapies in the brain. The sonication of larger volumes in patients with recurrent GBM will be investigated in a future trial using a larger SonoCloud device.

Ying Meng from Sunnybrook Health Sciences Centre discussed BBB opening in primary brain tumors. This was a safety and feasibility study with non-invasive MRgFUS. The objective of this phase I, single-arm open-label study was to assess the safety and feasibility of BBB opening with systemic chemotherapy using MRgFUS for the first time in patients with glioma. Five patients with previously confirmed or

suspected high-grade glioma underwent a single MRgFUS BBB opening with concurrent chemotherapy (n=1 liposomal doxorubicin, n=4 temozolomide) administration. Surgical resection of the tumor was performed the following day, and tissue samples of 'sonicated' and 'unsonicated' tissue were obtained for analysis where accessible. Participants continued with standard neuro-oncology care and were followed for three months. BBB opening within the target volume was confirmed with contrast-enhanced MRI, resolving within 20 hours. No adverse clinical or radiologic events occurred with BBB opening. Biochemical analysis of tissue from the tumor margin suggests evidence of chemotherapy delivery. In conclusion, MRgFUS BBB opening of peri-tumor tissue with concurrent administration of chemotherapy was well tolerated by patients with glioma. This study also demonstrated technical feasibility with the BBB closing within 24 hours post-sonication. The characterization of therapeutic delivery and clinical response to this treatment paradigm requires further investigation.

Travis Tierney from Nicklaus Children's Hospital presented on transcranial MRgFUS in the management of benign central intracranial tumors. The objectives of the trial were safety and feasibility of transcranial MRgFUS thermoablation for the treatment of benign centrally-located brain tumors in 10 children and young adults. Three patients have been treated so far including two cases of hypothalamic hamartoma remnant and one subependymal giant cell astrocytoma under general anesthesia. The study is open to subjects 8 to 22 years of age who require surgical intervention for a benign centrally-located brain tumor. The ExAblate 4000 system (Insightec) was used to target and thermally ablate target tissue. Successful thermoablation of target tissue was achieved in both hamartoma cases with immediate cessation of gelastic seizures. In both cases, durable cessation of epilepsy was accompanied by subjective improvement in mood and memory. Near-field calcium and acoustic cavitation events precluded complete thermal ablation of the subependymal giant cell astrocytoma in the third patient. No post-operative endocrine, cognitive or motor complications occurred in any case. In conclusion, FUS thermal ablation can be used safely to treat epilepsy associated with hypothalamic hamartomas. It is less certain that calcium-bearing tumors like subependymal giant cell astrocytomas can be treated with FUS. More work is necessary to further refine optimal patient selection criteria and definitively demonstrate the safety of FUS in treating other subcortical tumors in younger children.

Natasha Sheybani from the University of Virginia discussed FUS stimulation of glioma-derived extracellular vesicle release in vitro. Extracellular vesicles are characterized as a population of cell-derived vesicles ranging from 50 to 500 nm in size whose biological function remains unknown. Extracellular vesicles contain representative proteins, mRNA, miRNA, lipids, and DNA of their parent cell, pointing to a potential role in intercellular signaling. Given the emerging role of extracellular vesicles in signaling in the tumor microenvironment (TME), FUS-elicited changes in extracellular vesicle release from cancer cells could exert a strong influence on tumor biology. For hyperthermia experiments, GL261-luc2 murine glioma cells were seeded into Celartia PetakaG3-HOT chambers around 24 hours before FUS exposure (1.1 MHz, 252 sonications, 5 W input power, 5 s duration). For FUS plus microbubble cavitation experiments, Nunc OptiCell culturing devices seeded with U87-MG human glioma cells were supplemented with microbubbles immediately prior to FUS treatment. A 1 MHz unfocused transducer was positioned above the OptiCell, for insonation of cells at a PNP of either 300 or 500 kPa via raster scan (0.5% duty cycle, translation speed ~ 2.0 mm/s). Fifteen minutes following FUS exposure, supernatant was isolated and clarified for extracellular vesicle isolation. Both FUS-hyperthermia and FUS plus microbubbles cavitation elicited a statistically significant increase in extracellular vesicle release. PNP did not significantly impact extracellular vesicle secretion. Extracellular vesicle size distribution did not change significantly as a function of FUS exposure. Ongoing research using genomic profiling of glioma-derived extracellular vesicles suggests increases in markers of heat-shock proteins and exosome formation. Next steps will validate the prevalence of extracellular vesicle subtypes and evaluate whether thermal and mechanical FUS exposure differentially impact the proteomic profile of glioma-derived extracellular vesicles.

Bingbing Cheng from the University of Texas Southwestern Medical Center discussed BBB opening by FUS with nanobubbles in a F98 glioma-bearing rodent model. These experiments were conducted with

a single transducer (0.5 MHz) coupled with a hydrophone for acoustic feedback control (ultraharmonic emissions). A stereotactic device was used to perform the procedure without MRI guidance. At each brain target, stimulated acoustic emissions were monitored and controlled to a target threshold at an ultraharmonic frequency (0.75 MHz). FUS exposures were delivered in a 3x3 grid with 2 mm spacing to cover both the tumor and peritumoral region. Each target exposure was conducted at a 10 ms pulse length, 1 Hz PRF, 30 s duration under acoustic feedback control, and 0.05 AUC threshold. Tumor growth was measured using contrast-enhanced gradient echo MRI before and after FUS exposure. Immunohistochemistry at 6 hours, 24 hours, 3- and 7-days post-treatment was used to evaluate the brain response. The mean pressure using feedback control was 0.3 MPa. Within 6 hours, neurons had protein loss, but had started to recover by 3 days. In conclusion, this study demonstrated the feasibility of opening the BBB of the peritumoral region using FUS with nanobubbles under real-time acoustic feedback control in a GBM tumor-bearing rat model. The opening was robust and reliable across 40 rats by monitoring real-time acoustic emissions (ultraharmonics) of activated nanobubbles and adjusting the pressure accordingly throughout treatment. No damage was observed to neurons or astrocytes 3 days post-treatment.

Pavlos Anastasiadis from the University of Maryland discussed the development of a mouse model of GBM for improving FUS-mediated BBB opening for delivery of therapeutic agents. The objectives were to investigate FUS-induced changes in inflammation in the tumor core and the area of resection cavity. A transgenic mouse model was developed. Early MRI findings were consistent with low-grade glioma that develops into a larger late-stage glioma with heterogenous features. Histopathology demonstrated similar features to human glioma. Mice were treated with MRgFUS for BBB opening alone, and with various therapeutic agents. In conclusion, early data suggests the utility of the transgenic model.

Hiroyuki Kobayashi from Hokkaido University presented work investigating the effects of sonodynamic therapy on glioblastoma cells (F98) using a low frequency FUS device in combination with 5-aminolevulinic acid (5-ALA) as a sonosensitizer. 5-ALA is an endogenous non-protein amino acid and is the first compound in the porphyrin synthesis pathway, which is the pathway that leads to heme in mammals. Cultured F98 rat glioblastoma cells were co-incubated with 5-ALA four hours prior to FUS. Sonication was performed with a 220-kHz transcranial MRgFUS system (InSightec). To determine optimal parameters, sonication was performed with 1024 transducer elements under the following conditions: frequency, 220 kHz; total energy, 400 to 4000 J; output power, 10 to 20 W; duration of irradiation, 120 to 240 s; duty cycle, 10 to 100%. During sonication, target temperature was kept under 42°C. Cell proliferation assays showed a reduction of cell viability that depended on both duration of sonication and output power, but was not affected by duty cycle. There were no changes in cell morphology. FUS significantly induced apoptosis (caspase-3). In conclusion, in vitro data suggests the possibility that a lower total ultrasound energy can achieve cytotoxic effects using the 220-kHz transcranial MRgFUS system in conjunction with 5-ALA as compared to thermal coagulation by FUS alone. Induction of apoptosis was a key mechanism of cell damage. Further, efficacy of sonodynamic therapy was observed within the normal range of physiological temperature. Although various parameters need improvement, sonodynamic therapy may be a novel treatment strategy for malignant gliomas.

Michiharu Yoshida from Hokuto Hospital discussed sonodynamic therapy in a rat glioma model (F98) and the development of personalized treatment for FUS. In the first of two experiments, F98 glioblastoma rats were irradiated with 220 kHz transcranial MRgFUS (Insightec) combined with 5-ALA with the following parameters: total energy, 500 J; output power, 18 W; duration of irradiation, 30 s; duty cycle, 100%; target temperature under 42 °C following 100 mg/kg 5-ALA treatment, and the anti-tumor effects were assessed based on changes in tumor volume and histology. Rats treated with sonodynamic therapy had reduced tumor invasion without signs of damage to normal brain tissue. In the second experiment, fresh tissue from a patient with GBM was sequenced with next generation sequencing (target gene panels of 160 genes for cancer not specific to the brain, and 50 genes for brain tumors). Significant CDK4 amplification was detected and suggested a CDK4/6 inhibitor (such as palbociclib) might be

effective. The next step will be to determine the effectiveness of personalizing the therapeutic agent to administer with sonodynamic therapy and BBB opening. In conclusion, sonodynamic therapy with 220-kHz transcranial MRgFUS and 5-ALA can be safely used for the treatment of malignant glioma.

Francesco Prada from the Focused Ultrasound Foundation presented on sonodynamic therapy with fluorescein in a glioma rat model (C6). Fluorescein has recently emerged as an image-guided tool for surgical procedures as it selectively accumulates in glioma tissue. This study investigated the combined use of sonodynamic therapy with fluorescein (10 mg/kg) in a rat model of glioma (C6). Fluorescein washes out within 20 minutes. Sonication parameters were: 350 kHz single-element transducer, 20 mm focal distance, 10% duty cycle, 20-minute sonication. Peak pressure was applied at three different pressures: 0.03 MPa, 0.04 MPa, and 0.055 MPa. FUS combined with fluorescein slowed tumor growth at all three levels tested. Preliminary histology results suggest that increased power levels in combination with fluorescein may increase tumor cell necrosis and apoptosis. In conclusion, growth curves demonstrate that sonodynamic therapy with fluorescein improved tumor growth control. Determining the optimal intensity of FUS plus fluorescein that can induce apoptosis of glioma cells will allow sonodynamic therapy to be a potent and less invasive therapy for malignant glioma.

Pedro Norat from the University of Virginia discussed FUS treatment of cerebral cavernous malformations (CCMs). Current treatment options for patients with CCMs are observation or surgery, but the results are often less than favorable with 50% of patients experiencing cognitive deficits. A mouse model of CCM (endothelial knockout of the CCM1 gene) was developed to evaluate FUS for the treatment of CCM. Mice were treated with 5-ALA to assess if this drug collects into the caverns of the vascular malformation with the aim of using 5-ALA as a sonosensitizer. The CCM1 conditional knockout mouse generated cavernous malformations as expected. The addition of 5-ALA allowed for accumulation suggesting that this drug could be used as a sonosensitizer to focus a more robust dose of FUS to these mice with 5-ALA and MRgFUS.

Tyler Gerhardson from the University of Michigan spoke on histotripsy-mediated immunomodulation in a gl261 intracranial mouse glioma model. Histotripsy can induce tumor ablation in a safe and targeted manner within 5 mm of the skull surface. The objective of this study was to investigate the immune response of a mouse model of glioma (N=27) following histotripsy ablation of an intracranial GBM. A 1 MHz, 8 element transducer with aperture diameter of 58.6 mm and focal length of 32.5 mm was used for treatment. A phased array imaging probe was inserted coaxially within the transducer to allow tumor targeting and treatment monitoring. Fifty histotripsy pulses were applied through the skull to a single point within the tumor at a PRF of 1 Hz and an estimated PNP of 40 MPa. Treatment was applied 2 weeks after inoculation and mice were survived for 1 week after histotripsy treatment. Brain tumors, spleens, and lymph nodes were harvested for flow cytometry. In addition, immunohistochemistry staining was performed on the primary brain tumor. There was a reduction in myeloid suppressor cells (MDSCs), thought to play a role in immunosuppression, after histotripsy. There was a large increase in interferon gamma (IFN-γ), thought to activate tumor-specific immunity, in mice treated with histotripsy. In conclusion, changes in the immunomodulatory environment and tumor histology indicate that histotripsy can increase immunogenicity and anti-tumor response.

Natasha Sheybani from the University of Virginia discussed leveraging MRgFUS to potentiate immunotherapy for GBM. There are several hypothesized interactions between FUS and the cancer immunity cycle. This study investigated the effects of FUS BBB opening with microbubbles in a mouse model of glioma (GL261-luc) on the immune system. FUS plus BBB opening promotes dendritic cell maturity within the tumor, meninges, and tumor-draining cervical lymph nodes. It also increased anti-experienced, PD-1 expressing CD8+ T cells in the brain. However, other checkpoint blockade molecules like TIGIT and TIM3 were not affected by FUS. Glioma growth was restricted as early as 6 days following treatment. In conclusion, BBB disruption with FUS plus microbubbles can elicit mechanisms of immunity in a murine model of glioma independent of drug delivery. Ongoing studies aim to characterize the immune cells elicited by FUS plus microbubbles and to couple this approach with checkpoint inhibitors.

Anastasia Velalopoulou from the Georgia Institute of Technology presented on the effects of FUS-induced hyperthermia on immune cell infiltration. The objectives of this study were to investigate whether FUS-hyperthermia could induce an immune response in a mouse model of GBM (GL261-luc2). Mice were sonicated with a MRgFUS (1 MHz) custom-made device. Tissue was harvested 1 week after FUS treatment. FUS-hyperthermia increased infiltration of activated natural killer (NK) cells and effector CD8+ T cells. FUS-hyperthermia also enhances the CD8+/CD4+ ratio in the tumor microenvironment. In conclusion, FUS-induced mild hyperthermia modified the immunosuppressive milieu of the GBM tumor and ameliorates cytotoxic immune cell infiltration in the tumor.

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Panel Discussion: Sonodynamic Therapy

Panel Moderator: F. Prada
Panelists: H. Kobayashi, P. Norat, and M. Yoshida

The panel discussed their opinions on the following topics:

1. **All of the presentations mentioned using a dye as an intermediary for the sonodynamic therapy, is it necessary to include this step?**

   There was agreement that this is not necessary for efficacy of the treatment. 5-ALA accumulates in the mitochondria, and sonodynamic therapy induces loss of mitochondrial membrane potential resulting in cytotoxicity and loss of tumor cells.

2. **There was some discussion on the potential mechanisms of action for sonodynamic therapy.**

   One mechanism by which sonodynamic therapy acts on brain tissue is likely microbubble cavitation. Another proposed mechanism is the Haber Weiss reaction and the generation of reactive oxygen species that produces oxidative stress. Increasing iron concentrations may also enhance this kind of therapy.

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Cancer Immunotherapy

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

Natasha Sheybani from the University of Virginia discussed immunotherapy and FUS ablation for metastatic breast cancer. Immune rejection of breast cancer is very rare due to poor functional CD8+ T cell infiltration and immunosuppression in the tumor microenvironment. A syngeneic metastatic mammary carcinoma model in mice was used (4T1-HA) to model breast cancer. The cells express hemagglutinin for the purpose of elevated immunogenicity and tumor-specific T cell tracking. The goal of this study was to evaluate the hypothesis that ultrasound-guided FUS thermal ablation can serve as an auto-vaccine for the treatment of breast cancer with immunotherapy. Fourteen days after tumor implantation, tumors were partially thermally ablated with FUS using a 3 MHz single-element transducer (30 W for 4 s sonication). Tissues were collected 7 days following FUS and analyzed with histology and flow cytometry. FUS increased dendritic cells in draining lymph nodes, particularly CD86+ dendritic cells. FUS did not change tumor outgrowth rate or the infiltration of T cells into the tumor. Therefore, further experiments with FUS also administered gemcitabine, which is known to inhibit the contribution of myeloid-derived suppressor cells (MDSCs) to the immunosuppressive tumor microenvironment. Gemcitabine was administered at the same time as FUS followed by weekly treatments of gemcitabine alone. The combination of FUS and gemcitabine significantly restricted tumor outgrowth. Ongoing experiments are evaluating the contribution of the immune system to this effect.

Gail ter Haar from the Institute of Cancer Research presented a preclinical investigation of the immunological effects of pFUS and immune checkpoint inhibitors in pancreatic cancer. The objectives of this study were to investigate whether FUS could change immunogenicity in an orthotopic mouse model of pancreatic cancer (KPC). Mice were given immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1 (200 µg)) 3 days before FUS. Three hours following sonication, the mice received a second dose of immune checkpoint inhibitors (100 µg), and at 3, 6, and 9 days after FUS. Tissues were collected at day 12. PFUS plus checkpoint inhibitors inhibited tumor growth. The combination treatment had no additional effect on IFN-γ levels compared with checkpoint inhibitors alone. Levels of TNF-α were significantly higher after pFUS alone compared with any other treatment including the combination. PFUS and the combination increased levels of immune cells in lymph nodes. Additionally, there was an increase in survival in mice that received the combination treatment. In conclusion, the combination of pFUS and immune checkpoint inhibitors extends survival and controls tumor growth. A possible mechanism is that pFUS is destroying the tumor stroma and allowing immune cells to get into the tumor. Future work will look at underlying mechanisms and also combine pFUS with immunotherapy treatments.

George Schade from the University of Washington presented on immune system changes after histotripsy ablation of renal cell carcinoma (RCC). Boiling histotripsy is being developed as a non-invasive FUS treatment for RCC and is associated with short-term immunological changes in vivo such as altered circulating and intra-renal cytokines and increased infiltration of CD8+ T cells in the Eker rat model. The goal of this study was to characterize the long-term immunological changes after boiling histotripsy. Boiling histotripsy was delivered to 50% of the tumor. Following treatment, rats were recovered, underwent serial US imaging surveillance and serial blood draws, and were survived for 7, 14, or 56 days. Flow cytometry was performed on processed tissues and blood to analyze changes in circulating and local immune cell populations. Boiling histotripsy resulted in expected tissue homogenization. There were no changes in CD11+ dendritic cells. There was a significant elevation in T cell subpopulations; CD4+, CD62L-, and CD44+ effector memory T cells and a trend for an increase in central memory CD4+, CD62L+, and CD44- cells in tumor-draining lymph nodes. There were also increases in subpopulations of CD8+ T cells, and a significant increase in CD8+, CD62L-, and CD44+ effector memory cells in both tumor-draining lymph nodes and spleen and central memory CD8+, CD62L+, and CD44- cells in tumor-draining lymph nodes. There was a significant increase in intra-renal cytokines IFN-γ, IL-10, and TNF-α. In conclusion, boiling histotripsy ablation of RCC was associated with specific changes in the immune system. Future experiments will further characterize the long-term implications of these immunologic effects.

Marc Santos from the Sunnybrook Research Institute discussed an evaluation of the immune response following mouse brain tumor ablation with MRgFUS. The ability of different types of FUS to evoke an immune response has been previously established, suggesting its potential to augment immunotherapies. The objective of this study was to investigate the immune response of gliomas in mice (GL261) following MRgFUS. To reduce superficial heating, craniotomies were performed immediately preceding tumor cell implantation, and tumors grew for 14 days. MRgFUS was performed in a 7T MRI scanner using a preclinical MRgFUS system. A single-transducer system was used (focal length 20 mm; f-number 0.8) and driven at 5.5 MHz. Sonications were performed for 15 s at 2.45 W. Data was acquired at day 21 (7 days post-ablation or sham treatment) for tumor growth, histology, and flow cytometry. MRgFUS at 5.5 MHz was able to thermally ablate tissue, but some skull overheating was observed in a select set of animals. Tumor debulking was observed after MRgFUS. There was a significant increase in CD4+ cell density, but not CD8+, within the tumor boundary. In conclusion, MRgFUS shows potential for eliciting anti-tumor responses against an orthotopic tumor model of GBM in mice. MRgFUS ablation of mouse brain tumors is technically challenging and focused transducers operating at high frequency with low f-number are recommended (or phased array geometries).

Gadi Cohen from the National Institutes of Health presented on the immunological response of the tumor microenvironment after pFUS. The objective of this study was to assess the proteomic and transcriptomic profile changes in the tumor microenvironment of mouse breast cancer (4T1) and melanoma (B16) tumors following non-ablative pFUS treatment. First, a temporal expression analysis of cytokines, chemokines, and trophic factors in the tumor microenvironment of the mouse models without FUS was performed. Mice were euthanized at day 1, 3, 5, 7, 9, and 11 post-inoculation. There was a decrease in anti-tumor immunity factors such as IL-10, Il-1, or TNF-α in the melanoma model and a decrease in IL-1, IL-2, and TNF-α and an increase in intra-tumoral immunosuppression factors (VEGF) in the breast cancer model. Next, pFUS was used at 6 MPa and tumors were harvested at 1, 8, 24, 48, and 72 hours after treatment. An anti-tumor response in the tumor microenvironment was observed within 24 hours after FUS in the melanoma model along with a suppression in tumor growth. Similar results were seen for the breast cancer model. RNA-seq pathway analysis suggested an anti-tumor response in both tumor models after FUS treatment. In conclusion, the tumor microenvironment varies according to tumor type. These results suggested that FUS has the potential to act as a neoadjuvant altering the tumor microenvironment to stimulate an anti-tumor immune response.

Parwathy Chandran from the National Institutes of Health presented on immune cell modulation of pFUS in murine melanoma and breast cancer. The objectives of this study were to see if non-ablative pFUS can enhance immune cell infiltration and turn a 'cold' tumor into a proinflammatory 'hot' tumor in mouse breast cancer (4T1) and melanoma (B16) tumor models. PFUS was performed at 1 MHz and 6 MPa and tissues were collected at days 1, 3, and 5 post-treatment. Six MPa was chosen as the PNP after a preliminary study looking at a range of pressures found that at 6 MPa, DNA damage was occurring in tumor cells. PFUS reduced tumor volume. For melanoma cells, on day three there was immune cell infiltration into the tumor with a high influx of helper cytotoxic T cells, macrophages, and NK cell activity in the spleen. However, on day 5 these signals decreased in the spleen and increased in the lymph nodes. For breast cancer cells, there was a slow influx of helper T cells, cytotoxic macrophages, NK cells, and dendritic cells on day 5. There was also suppression of regulatory T cells, MDSC, PD-1, and CTLA-4. In conclusion, these results show that pFUS influences immune cell populations differently depending on tumor type. PFUS activated both innate and adaptive immune systems. Future work will optimize pFUS parameters to further enhance immune cell infiltration and slow tumor growth.

Sri Nandhini Sethuraman from Oklahoma State University discussed how calreticulin-nanoparticles synergize with FUS for enhancing the immune response to melanoma. Immunogenic cell death (ICD) in melanoma cells by expression of endogenous calreticulin (CRT) in tumor cells stimulates innate and adaptive immunity. The objective of this study was to investigate the combination of FUS with ICD-enhancing CRT-nanoparticles for the synergistic enhancement of immune effects in a murine melanoma model (B16). Three CRT-nanoparticle injections of 20 µg each were given 2 days apart, and FUS heating (43-45°C, ~15min; 1.5 MHz central frequency) was applied sequentially 24 hours after each injection to evaluate tumor regression. The combination of CRT-nanoparticles and FUS suppressed B16 melanoma growth in tumor-bearing mice. FUS increased the immunogenic priming ability of CRT-nanoparticles by increasing surface expression of CRT in tumors. The combination therapy augmented local and systemic immunity against melanoma and increased the ratio of M1 to M2 macrophages in the spleen. In a re-challenge experiment, the combination treatment group had slower tumor growth over 4 weeks. A vaccination study, in which in vitro melanoma cells were treated with FUS and CRT and then injected into mice, suggested that FUS was better at enhancing tumor-specific immunity than the combination treatment. In conclusion, CRT modulated both innate and adaptive immunity. The combination produced robust local and systemic 'abscopal' anti-tumor effects.

Kensuke Kaneko from Duke University presented on single-cell RNA-sequencing analysis of HIFU-treated breast cancer. Mechanical HIFU (M-HIFU) induced stronger anti-tumor immune responses than conventional thermal HIFU (T-HIFU) in a murine colon cancer model. The objectives of this

study were to assess both methods in a murine breast cancer model (MM3MG HER2) as a way to induce immune checkpoint blockade. Established tumors were treated using a 1.5 MHz HIFU transducer under two different protocols (50% duty cycle, 1 Hz PRF, 20 W, 10 s or 2% duty cycle, 5 Hz PRF, 200 W, 20 s) to produce either thermal necrosis or mechanical lysis of the tumor cells 7 days after inoculation. M-HIFU significantly suppressed tumor growth compared with T-HIFU, and improved survival in mice. M-HIFU also significantly increased HER2-specific cellular immune response. Flow cytometry analysis revealed that M-HIFU treatment improved infiltration of immune cells in tumors, including T cells and NK cells. M-HIFU treatment increased immune checkpoint molecules on immune cells, such as PD-L1. Single-cell RNA-sequencing of immune cells demonstrated increased expression of co-stimulatory and cytotoxic markers of CD8+ T cells in the M-HIFU-treated group. A second experiment was conducted with the combination treatment of M-HIFU with PD-1/PD-L1 blockade for MM3MG-HER2 tumor-bearing mice, and demonstrated that the combination strategy induced a significantly increased HER2-specific immune response and anti-tumor efficacy compared with either treatment alone. In conclusion, M-HIFU showed higher anti-tumor efficacy than T-HIFU in a murine breast cancer model. Combining M-HIFU and anti-PD-L1 antibody demonstrated enhanced anti-tumor cellular response and prolonged survival of tumor-bearing mice.

Frederic Padilla from INSERM discussed FUS for myeloid cell modulation and repolarization in breast cancer. The objective of this study was to evaluate whether FUS can impact the representation and polarization of myeloid cells in a murine model of metastatic breast cancer (4T1). This syngeneic mouse breast cancer model is known to have a strong hematopoietic cell infiltrate consisting predominantly of Gr-1+/CD11b+ myeloid cells that have been profiled as MDSCs capable of inhibiting specific T-cell-mediated tumor immunity. Mice were exposed to one of three different ultrasound exposure conditions targeting 50% tumor volume: boiling histotripsy, thermal ablation, or microbubble destruction. In a separate round of experiments, these FUS regimens were compared with single fraction radiation therapy. At 7 days post-treatment, there were no effects on tumor weight. Both thermal ablation and radiation therapy increased MDSCs. The mechanisms that cause this effect with thermal ablation are unknown. Radiation therapy is known to increase the production and release of cytokines and chemokines, and perhaps a similar effect is caused by thermal ablation. In conclusion, preliminary results report a relatively weak impact of FUS monotherapy on the myeloid compartment in 4T1 tumors, with the exception of thermal ablation impacting MDSCs.

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Panel Discussion: Cancer Immunotherapy

Panel Moderator: J. Foley
Panelists: C. Arvanitis, D. Brenin, K. Ferrara, J. O'Donnell-Tormey, F. Padilla, and R. Price

The panel discussed their opinions on the following topics:

1. **Preclinical work comparing the immunogenicity of different FUS modalities (boiling histotripsy, pFUS, etc.) is ongoing. Can any conclusions be drawn from these investigations?**

   The best FUS modality that can stimulate the immune system is unclear at this time. In the clinical trials, treatment is occurring with the devices available for human use. However, preclinical results don't always translate to the human condition, so the clinical applicability of the results from these comparative studies remains to be seen. Mechanical FUS shows some superiority in early results. There remain many interesting questions. For example, are there certain immune responses that are preserved across tumor types? Another way of looking at this is to ask whether there are certain tumor microenvironments that are sensitive to thermal or mechanical effects. Further knowledge on the mechanisms involved with FUS modulation of the tumor microenvironment is

necessary. This knowledge could also lead to optimization of potential therapeutics to combine with FUS. The panel also discussed the importance of the ablated tumor volume, and that partial versus complete thermal ablation may produce different tumor responses.

2. **Radiation therapy in combination with immunotherapy is increasingly studied. Is there any knowledge from those experiments that could influence FUS combination treatment selection?**

   The panel agreed that FUS researchers should capitalize on combinations that work with radiation therapy. For example, pancreatic cancer research suggests that anti-CTLA-4, anti-PD-1, and anti-CD40 combinations are effective. Another option is to investigate known mechanisms of immune modulation delineated with radiation therapy and see if the mechanisms are similar for FUS instead of doing very broad investigations.

3. **While tumor tissue samples pre- and post-treatment remain the gold standard for assessing efficacy, are there any non-invasive methods in development that could replace the need for invasive procedures.**

   There may be imaging biomarkers that can help investigate the immune response with FUS treatment. Research suggests that following CD8+ T cells over time after treatment with immunotherapy might be useful. There are also several additional clinically-relevant methods for other immune cells such as macrophages. For patients with prostate cancer that are undergoing FUS, there is no opportunity for biopsy samples from the tumor. In this case, immune responses will be measured through blood sampling at various time points before and after the procedure.

4. **When combining an experimental FUS procedure with an experimental therapeutic agent, there can be significant regulatory challenges. Is the future of the combined FUS and immunotherapy approach limited to therapeutic agents that have already received FDA approval?**

   Panelists agreed that the FDA's decisions have not been consistent and are dependent on individual situations. Depending on the study design, sometimes the FDA has considered the procedure a new device or a new drug. Moving forward it is important to work with the FDA early in the development of the study protocol. However, there is currently exponential growth in the number of FDA-approved immunotherapy agents that can be combined with FUS.

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Liver/Pancreas/Kidney

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 respiratory motion.

Cyril Ferrer from the University Medical Center Utrecht presented on combined self-scanned/gated MR-HIFU treatment of the pancreas. HIFU ablation of a moving pancreas is feasible, but remains challenging due to respiratory motion. The objectives of this study were to simulate the combination of a self-scanned/gated approach and use acquired 4D-MRI data to distinguish locations where self-scanned sonications (fixed HIFU sonications combined with respiratory motion to passively scan the target) could be used from those that should be targeted with gating. Through 4D-MRI data, the target displacement was evaluated in 3D throughout the respiratory cycle using image registration. Self-scanned sonications were attributed to locations where the target is always present, otherwise the gated approach was used. For all locations, thermal doses were simulated based on the bio-heat transfer equation. A voxel-wise optimization selects a set of locations to achieve complete ablation of the target. Using data from six healthy volunteers, the number of sonications needed to ablate the pancreas head were calculated. Fewer sonications were estimated for the combined strategy compared to gating alone. In conclusion, a combined self-scanned/gated sonication strategy that exploits

respiratory motion may reduce the number of sonications required to ablate a target volume in the pancreas and potentially reduce treatment time.

Yak-Nam Wang from the University of Washington discussed MRI biomarkers for FUS treatment of pancreatic ductal adenocarcinoma. Previous preclinical research in a transgenic mouse model of pancreatic ductal adenocarcinoma (KPC mouse) demonstrated that pFUS disrupts dense fibrotic stroma and increases chemotherapeutic penetration. The objectives of this study were to implement non-invasive MRI methods to assess pFUS treatment effects in pancreatic ductal carcinoma. Three mouse models of pancreatic ductal carcinoma (subcutaneous, orthotopic, and transgenic) were evaluated with multi-parametric MRI at 14T to assess tumor response to ultrasound-guided pFUS treatments or sham treatments. MR images were collected 48 hours before pFUS and post-pFUS therapy. Maps for T1 and T2 relaxation, apparent diffusion coefficient, magnetization transfer ratio, and chemical exchange saturation transfer for the amide proton and glycosaminoglycan spectrum were generated. Tumors were excised and prepared for histological and biochemical evaluation. Cavitation activity was achieved in all three mouse models. Mean glycosaminoglycan spectrum and T2 map quantitations decreased significantly post-treatment only for the transgenic mouse group (KPC). Hyaluronan concentrations were lower in all three pFUS groups. In conclusion, there was a significant decrease in glycosaminoglycan spectrum and T2 values, likely driven by changes in hyaluronan and the associated liberation of complex water molecules from within the tumor stroma. The increase in apparent diffusion coefficient likely reflects increased diffusivity within the treated pancreatic ductal carcinoma.

Maria Karzova from Moscow State University presented on a comparison of Sonalleve V1 and V2 MR-HIFU in abdominal tumors. Boiling histotripsy can generate shock fronts greater than 100 MPa in bovine liver. The amplitude of the shock front is dependent on the array geometry. The goal of this study was to characterize the Sonalleve V2 therapeutic array in order to evaluate its capability to produce shock waveforms at the focus required for boiling histotripsy. The V2 array is less uniform than the V1 and is divided into sectors. The V2 has a longer focal lobe along the axial direction (z) but the same sizes along the transverse directions x and y. Acoustic characterizations were carried out using hydrophone measurements in water. Simulations of focal waveforms demonstrated that the V2 system produces fully developed shocks at a lower amplitude (82 MPa) than the V1 system (92 MPa). In conclusion, the V2 system has a smaller focusing angle and produces shocks with amplitudes that are about 10 MPa lower at the same power. This should be considered when developing treatment protocols for shockwave exposures like boiling histotripsy.

Joan Vidal-Jove from Hospital University Mutua Terrassa discussed MRgFUS in patients with liver cancer. This talk described the experience of treating malignant primary and metastatic liver tumors with thermal ablation at a single institution. Around 200 cases underwent tumor ablation from February 2008 to May 2016. Included patients were not candidates for surgery or other ablation modalities such as radiofrequency ablation, microwave ablation, or embolization. The first 40 patients were analyzed. Most patients continued on systemic chemotherapy treatments following the ablation procedure. Total treatment time varied between 60 and 180 minutes. There were difficulties related to patient positioning and access to segments VII and VIII, and real-time response evaluation prolonged the procedures. Major complications included grade III skin burns that required plastic surgery, and costal osteonecrosis. In conclusion, MRgFUS is an effective and safe method for ablation of malignant primary and metastatic hepatic tumors. In liver tumors, limitations of the available devices prevent access to some lesions compared with other ablation modalities. Access to deep lesions could increase the use of MRgFUS ablation.

Cynthia Anderson from the John A. Burns School of Medicine presented on HIFU for hepatic gene transfer in a mouse model. The goal of this study was to evaluate the potential for HIFU to enhance the efficiency of hepatic gene transfer. Integration of HIFU into the current ultrasound targeted microbubble destruction technique may improve gene transfer efficiency by enhancing transient vascular permeability in the liver. Gene-expression vectors were bound to the shells of lipid microbubbles and

deposited in the liver by acoustic cavitation. Previous experiments with unfocused ultrasound demonstrated that a plasmid containing human blood coagulation factor IX (hFIX) was delivered to the liver and reduced blood clotting time. Bioluminescence and immunofluorescence were used to determine hepatic transfection efficiency and the distribution and intensity of reporter expression. The effects of HIFU exposure at different planes in the medial and left liver lobes for the various ultrasound parameters and targeting depths (5-18mm) were compared with histology. The HIFU device was a 1 MHz single-element transducer (Sonic Concepts). Ultrasound parameters were identified in unfocused ultrasound studies that produced site specific transfection of hepatocytes with plasmids encoding reporters without substantial damage in the livers of wildtype and Hemophilia B mice. Using the new HIFU-based strategy, similar levels of reporter expression compared to the unfocused technique 24 to 48 hours after transfection were observed. Robust clusters of reporter gene expression were observed in distinct regions of the liver after HIFU compared to the diffuse pattern of expression observed for unfocused treatments. Increasing the HIFU PRF (50-60 Hertz range) with short pulse durations of less than 20 μs produced the greatest average radiance for reporter expression. In summary, a HIFU protocol was developed that minimizes tissue bioeffects. Future work will use this protocol to explore the efficacy of HIFU-targeted microbubble destruction to deliver gene therapy for Hemophilia B and familial hypercholesterolemia.

Cesare Gagliardo from the University of Palermo presented on MRgFUS of the liver under respiratory motion in an animal model. A novel treatment software (TRANS-Focused Ultrasound in Moving Organs (FUSIMO)) has been developed to support MRgFUS treatment of liver lesions through electronic real-time beam steering of the ultrasound transducer. Prior to clinical use, an in vivo preclinical trial using the TRANS-FUSIMO treatment system to evaluate the safety and the technical efficacy and efficiency of the generation of pre-defined necrotic lesions in the healthy liver was carried out. These experiments used an improved non-clinical prototype of Insightec's conformal bone system integrated with a 1.5T MRI. A set of interventional flexible coils was used for optimal imaging. All experiments were performed in a sedated porcine model. During each sonication, real-time multi-reference thermal monitoring was achieved using a 3 mm isotropic EPI-GRE slice (8 Hz). Liver lesioning was possible during both breath-hold and ventilator-controlled breathing due to the motion compensation algorithm allowing controlled electronic steering according to MRI images. Animals were sacrificed, lesions confirmed with visual examination of the liver, and necrotic tissue identified in the liver.
In conclusion, the TRANS-FUSIMO animal trial is still ongoing but preliminary results were achieved using the motion compensation algorithm. It was possible to confirm FUS-induced lesions with both contrast-enhanced MRI and post-operative pathological examination. The TRANS-FUSIMO treatment system is capable of compensating for liver motion under ventilator-controlled respiration through real-time MRI motion detection and real-time FUS beam steering.

Andrea Cafarelli from the BioRobotics Institute presented on ultrasound-guided robotic strategy for FUS treatment of moving organs. The management of respiratory motion of abdominal organs remains a challenge for FUS. The objectives of this study were to assess an innovative tracking strategy to compensate for respiratory motion of moving organs under US monitoring with the robotic platform FUTURA (http://www.futuraproject.eu). This strategy sonicates a moving target by using an angular motion with a robotic manipulator holding the HIFU transducer (around a fixed pivot point), while adjusting the focal depth continuously with the axial electronic steering capabilities of an annular transducer. A machine-learning detection pipeline identifies relevant patches in MRI images. Ultrasound image guidance and robotic manipulators were used to automatically track, detect, and correct for target motion throughout the entire treatment. US imaging was used to estimate and learn the periodic trajectory of the target and to monitor treatment success in real time. The system was tested in a model of skin-contact control using an abdomen simulator and a chicken breast. The sonication parameters were: 1.2 MHz frequency, 115 W power, 20 s duration. The tracking error between the target point, chosen from US images, and transducer focus position was always lower than 1 mm. In conclusion, a continuous FUS sonication without breathing suppression techniques can target abdominal organs.

Vesna Zderic from George Washington University discussed ultrasound-induced insulin release as a potential treatment for type 2 diabetes. Previous research showed that therapeutic ultrasound is capable of stimulating insulin release from pancreatic beta cells. The aim of this study was to investigate the translational potential of therapeutic ultrasound as a novel treatment for type 2 diabetes via preliminary in vitro and in vivo studies. In vitro studies were used to determine the optimal frequency (1 MHz) that could stimulate insulin release without causing cellular damage. In vivo studies were carried out in wildtype human islet amyloid polypeptide (hIAPP) +/+ mice that were randomly assigned to either ultrasound treatment or the sham group. The ultrasound treatment group received one five-minute treatment of continuous 1 MHz ultrasound at 1 W/cm2 every 7 to 12 days. Blood samples were analyzed to determine blood insulin levels. After sacrifice, the internal abdominal organs, particularly the stomach, liver, and large intestines, were examined for any signs of external damage. Preliminary studies in a diabetic mouse model indicated no gross damage, including skin burns, in the treatment area. Treatment with ultrasound resulted in a statistically significant increase in blood insulin concentration; however, blood glucose concentrations were quite varied, and no conclusions could be drawn. Current work is focused on finding the optimal acoustic window for FUS application in patients with varying body mass index and whether extracorporeal treatment is feasible or whether an implanted device will be required.

Brian Lang from the University of Hong Kong presented on HIFU treatment for thyroid, and immune functions of benign thyroid nodules. The aim of this study was to investigate the effect of HIFU on local thyroid function and immune-related cytokines in patients with benign thyroid nodules. From 2017 to 2018, consecutive patients who underwent a HIFU ablation (Theraclion) for a benign thyroid nodule within a single session under IV sedation were analyzed (N=25). Venous blood samples were collected 1 hour before treatment (baseline), during treatment when the target volume had been ablated by 50%, immediately after treatment, and 96 hours after treatment. Serum thyroid stimulating hormone (TSH), Free T4, thyroglobulin, anti-thyroglobulin and anti-thyroid peroxidase auto-antibodies, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as levels of tumor necrosis factor (TNF) and interleukin-6 (IL-6) were measured. There were no differences in levels of TNF or IL-6 after treatment. Similarly, there were no differences for levels of ESR or CRP. However, serum TSH dropped significantly after treatment and this persisted for 96 hours. Free T4 had similar results. Thyroglobulin levels were significantly elevated 96 hours after treatment. In conclusion, during the early post-ablation period (96 hours post-ablation), HIFU ablation may have a greater effect on the thyroid gland itself than a systemic effect.

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Bone

Presentations described the use of FUS in clinical studies for the treatment of osteoid osteoma and bone metastases.

Alessandro Napoli from Sapienza University of Rome presented on MRgFUS for the management of osteoid osteoma. Preliminary studies have demonstrated the efficacy of MRgFUS in treating osteoid osteoma. The objective of this study was to demonstrate that non-invasive radiation-free ablation of osteoid osteoma with MRgFUS is a safe, effective, and durable treatment option. Patients with typical clinical and radiological findings of osteoid osteoma, suitable for MRgFUS and anesthesia, were enrolled in this dual-center prospective observational study. Safety (rate of complications), clinical effectiveness (visual analog scale (VAS) pain score reduction) and durability (stability of results over time) of MRgFUS were evaluated as primary outcome measures. Patients (N=45) were followed for at least 3 years. Overall, after MRgFUS treatment 87% of patients reached and maintained stable (pain free) during follow up. There were no adverse events observed during this study. In summary, this study demonstrated durable outcomes with a good tolerance profile.

Adam Waspe from the Hospital for Sick Children discussed progress toward a FUS osteoid osteoma treatment registry. Although the initial treatment effects of MRgFUS on osteoid osteoma have been promising, it remains a small volume procedure with variable patient selection, targeting, treatment parameters, outcome metrics, and follow up. An osteoid osteoma registry is an extremely important vehicle to collate a sufficient cohort of patients from multiple centers to demonstrate efficacy, but also to optimize and standardize the treatment. The Focused Ultrasound Osteoid Osteoma Treatment Registry was launched in 2018. The registry collects patients' demographic information and previous medical history, characteristics of osteoid osteoma treatment (imaging, patient reported pain, quality of life, and medication usage), procedure techniques and safety, and age-based outcome measurements (pain, quality of life). The goal is to use the data collected in the registry to compare FUS with other treatment modalities. A web-accessible prospective database was created using Research Electronic Data Capture (REDCap) software. There are currently two registries for osteoid osteoma, a FUS registry and a percutaneous registry that is affiliated with the Society for Pediatric Interventional Radiology (SPIR). The SPIR registry is collecting data on all osteoid osteoma procedures, except FUS. The FUS registry will have 9 sites and the SPIR registry will have 34. The FUS registry was designed to be the initial step in creation of a computational data center and registry to capture information on multiple types of FUS research.

Matthew Bucknor from the University of California, San Francisco presented results from a cost-effectiveness analysis of MRgFUS for palliation of painful bone metastases. The objective of this study was to determine if palliation with MRgFUS in patients with refractory pain from bone metastases is cost-effective (incremental cost-effectiveness ratio (ICER)), for a 24-month time horizon, from a health system perspective compared with medication. A Markov state transition model using TreeAgePro® was constructed to model costs, outcomes, and cost-effectiveness using data derived from a combination of the available literature, expert opinion, and reimbursement data at two US medical centers performing MRgFUS. In the model, costs, and quality adjusted life years (QALYs), discounted at a rate of 3% per year, were accumulated each month over a 24-month time horizon. Insurance reimbursement for MRgFUS was estimated to be between $16,500 to $17,000. Medication for pain palliation (Oxycontin) was estimated at $430 per month (25% increasing every 3 months due to tolerance over time). Other probabilities were estimated from the literature. Willingness-to-pay level was estimated at $100,000/QALY. In the base case analysis, MRgFUS treatment strategy cost an additional $8756.23 over the two-year time horizon to accumulate an additional 0.22 QALYs, equal to a $40,150.20 per QALY, thus making MRgFUS the preferred strategy. One-way sensitivity analyses demonstrated that for the base case analysis, the crossover point at which medication only would become the preferred strategy is $25,711.58 per treatment. The percentage of patients repeating MRgFUS and decreasing MRgFUS efficacy do not significantly affect the preferred strategy. The limitations of this analysis include (1) that the model did not account for treatment eligibility regarding the site of metastasis, (2) the estimation of the probability of symptom relief or recurrence was limited by the number of trials and varying lengths of follow up, and (3) there was a lack of MRgFUS-specific quality of life data. In conclusion, the base case and sensitivity analyses demonstrated that MRgFUS was a preferred treatment strategy across a wide range of transition state probabilities, costs, and QALYs.

Pavel Yarmolenko from Children's National Medical Center discussed the safety and feasibility of osteoid osteoma ablation with MRgFUS compared to radiofrequency ablation standard of care. Radiofrequency ablation is the current standard of care for definitive treatment of osteoid osteoma, but has several potential complications including bleeding, infection, skin and muscle burns, nerve injury from drilling through tissue, and heating along the radiofrequency ablation probe. The objectives of this study were to evaluate feasibility and safety of MRgFUS treatment of symptomatic osteoid osteoma, and to compare clinical response with standard of care radiofrequency ablation treatment. Analgesic requirement, VAS pain score, and sleep quality were used to evaluate clinical response. Nine patients with symptomatic extremity osteoid osteoma (7 males, 2 females; 16±6 years old) were treated with

MRgFUS without technical difficulties or any serious adverse events. There was a significant decrease in median pain scores four weeks after treatment. In the radiofrequency ablation group, nine patients (8 males, 1 female; 10±6 years old) were treated. All nine patients demonstrated complete pain resolution and cessation of medications by four weeks with significant decreases in median pain scores. In both groups, treatment response remained constant over the 1-year follow-up period. Procedure times and treatment charges were comparable between the two groups. In conclusion, this study demonstrates that MRgFUS ablation of osteoid osteoma refractory to medical therapy is feasible and can be safely performed in pediatric patients. The clinical response following MRgFUS ablation is comparable with standard of care treatment of osteoid osteoma over the course of a 1-year follow up, but without any incisions or ionizing radiation exposure.

Alessandro Napoli from Sapienza University of Rome presented results from a comparison of MRgFUS versus external-beam radiation therapy (EBRT) in patients with metastatic non-spinal bone disease. Previous clinical research demonstrated that MRgFUS reduced pain from bone metastases. The purpose of this study was to examine and compare the clinical outcomes of MRgFUS and EBRT in patients with painful bone metastases. Included patients (N=233) were randomly assigned (1:1 ratio) to receive MRgFUS or EBRT and outcomes were assessed at 4 weeks, 3 months, and 6 months post-procedure. There were no statistically significant differences in average pain, pain interference with activity, break-through pain, mood, or quality of life between arms. In conclusion, MRgFUS represents a valid treatment option and could be routinely introduced in the management of painful bone metastases that are accessible. The main advantages are that MRgFUS provides more rapid pain relief in the absence of ionizing radiation, toxicity, and adverse events. MRgFUS can also be administered concurrently with chemotherapy.

Chrit Moonen from University Medical Center Utrecht described the study plan for a clinical trial of FUS and radiotherapy for palliative pain treatment of bone metastases, also known as the FURTHER project. Previous research demonstrated that MRgFUS is a safe and effective treatment for alleviating pain from bone metastases. Eligible patients will be those who are ineligible for, or who failed or declined, radiation. The aim of the study is to demonstrate the efficacy and cost-effectiveness of MRgFUS compared to EBRT as a palliative treatment option to relieve bone pain caused by metastases. The study is designed to demonstrate that short-term pain relief is superior in treatment regimens with MRgFUS (alone or in combination with EBRT) as compared to standard of care treatment with EBRT. The primary outcome of the trial will be pain at 14 days post-treatment randomization. This study will also develop a prediction model to identify patients who are likely to benefit from MRgFUS or radiotherapy in order to allow effective use of the treatment. The project will begin enrolling patients in 2019. In conclusion, the FURTHER project aims to demonstrate that MRgFUS is a standard first-line treatment alternative to EBRT.

Alessandro Napoli from Sapienza University of Rome presented results on MRgFUS for oligometastatic prostate cancer bone metastases. The aim of this study was to assess the efficacy of local tumor control and safety of MRgFUS for bone lesions in patients with oligometastatic prostate cancer. Secondary aims were to assess pain control and overall survival. After treatment all patients (N=11) had a reduction in tumor volume as measured by PET/CT. Progression-free survival was 52.3 months, and overall survival was 62.9 months. Pain control was also observed. In conclusion, MRgFUS has preliminary safety and efficacy for tumor control of bone metastases in patients with oligometastatic prostate cancer. Further study is needed to confirm these preliminary results, identify factors predictive of treatment outcome, and select patients most likely to benefit from this treatment.

Sin Yuin Yeo from Klinikum der Universitaet zu Koeln presented data on early clinical experiences with MR-HIFU ablation for bone pain palliation. MR-HIFU ablation has previously been shown to reduce bone pain. This presentation described early clinical experiences using MR-HIFU ablation for bone pain palliation. Eight patients experiencing bone pain due to bone metastases (4), soft tissue sarcoma

with osteolysis (2), osteoid osteoma (1) and desmoid tumor (1) were treated with a Sonalleve® MR-HIFU system. The lesions were treated with acoustic powers between 40 and 170W. VAS pain scores were measured before and 3 months post-treatment. All patients experienced decreased pain scores. There were no treatment-related complications. In conclusion, early clinical experiences demonstrated that MR-HIFU ablation is a safe and effective alternative treatment for bone pain.

Daniele Mercatelli from Rizzoli Orthopaedic Institute presented on the treatment of painful bone tumors using MRgFUS with the conformal bone system. Some bone lesions are difficult to treat with MRgFUS due to positioning problems and lesion accessibility. The conformal bone system (Insightec) integrates new features that could help treat bone lesions in difficult to reach locations using conventional MRgFUS systems or other devices. The objectives of this study were to report single-center experience (Rizzoli Orthopaedic Institute) in treating painful bone lesions using the conformal bone system. The primary endpoint was efficacy (pain palliation at 3 months), and the secondary endpoint was safety. Ten procedures were performed in nine patients. At 6 months, 7 out of 9 patients experienced a significant reduction in pain. There were no adverse events observed in this study. In conclusion, MRgFUS with the conformal bone system is a safe and effective procedure for pain palliation in patients with bone lesions at locations that are not easily accessible with conventional MRgFUS systems.

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Panel Discussion: Osteoid Osteoma

Panel Moderator: A. Napoli
Panelists: M. Bucknor, P. Ghanouni, A. Napoli, A. Waspe, and P. Yarmolenko

The panel discussed their opinions on the following topics:

1. **What are the next steps for FUS treatment of bone applications?**
   Further treatment of benign bone conditions should be explored. One example is pain associated with bone marrow granulomas. Patients want non-invasive treatment options. Another interesting area with potential is using MRgFUS to focally deliver therapeutics to sarcomas.

2 **How important is temperature monitoring of bone with MR thermometry?**

   Temperature monitoring is important for both safety and efficacy. It's essential to measure temperature on the surface of the skin. It is also possible to achieve good temperature readings of the bone itself, particularly for younger patients. Younger bone marrow has different properties that allow for optimal temperature mapping during the procedure. Technical advances, such as using different arrays of coils, would allow for better signals in older patients.

   There are also situations where temperature monitoring has not proved necessary. For example, in patients that are cachectic and lack muscle tissue near the bone, targeting can be achieved with MRI imaging. A case of a patient with a metal implant near the tumor was also described; the tumor was treated with MRgFUS by targeting with imaging alone.

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Wednesday
October 24, 2018

Oncology *continued*

Prostate

Prostate tissue ablation with FUS was FDA approved in 2015. Presentations focused on methods to improve current techniques as well as additional methods of tissue ablation.

Clare Tempany from Brigham and Women's Hospital discussed initial experiences and follow up from a multicenter trial of MRgFUS for the focal treatment of localized prostate cancer. Patients with either low or intermediate-risk prostate cancer were included in the trial. The aim of the study was to establish the safety and feasibility of MRgFUS focal ablation for localized prostate cancer. To date, 39 men have been enrolled and treated at 7 sites. Patients will be followed for 2 years post-treatment. One serious adverse event occurred, which was a biopsy-related rectal hemorrhage that was temporary and resolved spontaneously. Other minor side effects include hematuria, urinary tract pain, and fatigue. In conclusion, early results suggest the safety of MRgFUS for prostate cancer. Accrual is ongoing, and more results are expected in the next few years.

Aytekin Oto from the University of Chicago discussed MRI-guided trans-urethral ultrasound ablation (TULSA) for patients with localized prostate cancer. TULSA uses a minimally-invasive ultrasound applicator to emit directional high-intensity ultrasound from within the prostatic urethra, to achieve conformal ablation of targeted prostate tissue under real-time MR-thermometry feedback control. The procedure uses a trans-urethral applicator with 10 ultrasound transducer elements. MR-thermometry acquired continuously during treatment is used to control the ultrasound power, frequency, and device rotation rate, to achieve a desired three-dimensional ablation pattern. This technique actively compensates for changes in tissue and blood flow. Preliminary safety and efficacy results from the TULSA-PRO Ablation Clinical Trial (TACT) pivotal study of whole-gland ablation for patients with mostly intermediate-risk localized prostate cancer were reported. The primary safety endpoint was the frequency and severity of adverse events during the first 12 months. The primary efficacy endpoint was the proportion of patients achieving a prostate-specific antigen (PSA) reduction. The primary efficacy endpoint of PSA decrease was achieved in 95% of patients. There were no rectal injuries or urinary incontinence. Serious adverse events occurred in 7% of patients. The most common serious attributable adverse events were grade 2 urinary retention (n=3) and grade 3 infection (n=3); all resolved. In conclusion, preliminary data from the TACT pivotal study of MRI-guided TULSA suggests safety and efficacy with a low rate of serious adverse events.

Cyril Lafon from LabTAU, INSERM presented on salvage high-intensity focused ultrasound (S-HIFU) for locally recurrent prostate cancer after definitive brachytherapy. The objective of the study was to evaluate the oncologic and functional outcomes of S-HIFU for locally recurrent prostate cancer after low-dose rate brachytherapy. The primary outcome measure was progression-free survival (PFS), defined as an absence of both biochemical failure and the introduction of adjuvant therapy. Fifty patients were enrolled in the study. Initially, patients were treated using dedicated post-EBRT parameters (n=13). Since May 2008, specific post-brachytherapy parameters were applied, considering devascularization and fibrosis created by brachytherapy (n=37). The median follow up was 4.6 years. The median PSA nadir after S-HIFU was 0.3 ng/ml. After 6 years, PFS was 41%. Metastasis-free survival was 75% after 7 years. Post-brachytherapy compared to post-EBRT parameters reduced grade 2/3 incontinence. Before S- HIFU, 25 patients had international index erectile function (IIEF)-5 scores of greater than or equal to 17, and this was maintained in 48% of patients at 1 year. Adverse events included incontinence, bladder outlet obstruction, and rectourethral fistulas. In conclusion, the results suggest that S-HIFU has demonstrated efficacy for the treatment of local recurrence after brachytherapy.

Jürgen Jenne from Fraunhofer MEVIS discussed advanced software support for MRgFUS treatment of prostate cancer. Therapeutic ultrasound for tissue ablation under US- or MR-guidance has shown very promising results, but is not integrated into an efficient and safe workflow. With better detection of

localized prostate cancer, there is a greater demand for treatments along with a greater number of treatment options. The aim of this study was to analyze the MRgFUS therapy workflow and to develop software tools to improve MRgFUS therapy of prostate cancer. Software tools based on MeVisLab (Medical image processing and visualization toolkit, MeVis Medical Solutions) with several dedicated C++ modules for image processing were developed. Advanced, 2D and 3D image viewers for detailed planning were created. An automated and interactive segmentation tool based on machine-learning algorithms was added to support the therapy planning stage. A quasi real-time prostate tracking software module working on MR-thermometry images was implemented to detect prostate deformation and motion during the course of therapy. Additionally, an automated quality assurance (AQUA) module was developed to detect unwanted parameter/protocol changes, occurrence of non-matching between the actual and reference images, and prostate motion that exceeds a pre-defined level. In conclusion, image processing tools have been developed that may simplify, speed up, and improve the precision of prostate MRgFUS.

Vera Khokhlova from Moscow State University presented on boiling histotripsy for mechanical ablation of prostate tissue. Compared to thermal ablation, boiling histotripsy has potential clinical advantages as it minimizes heat-sink effects and thermal spread, and it allows for real-time ultrasound feedback during and after the treatment via the appearance of echogenic bubbles at the focus and through production of a hypoechoic lesion. Previous research has successfully been used in preclinical studies to fractionate kidney and liver tissue ex vivo and in vivo. The goal of this study was to test the feasibility of boiling histotripsy ablation of fresh ex vivo human prostate tissue as a proof of principal for treating benign prostatic hyperplasia and prostate cancer. Fresh human prostate tissue samples were obtained via rapid autopsy (24 hours after death, N=4) using an IRB-approved procurement program. Boiling histotripsy pulses (10 ms duration, 1% duty cycle, peak focal pressures of p+=88 MPa, p-=17 MPa, 100 pulses/focus) were delivered to a rectangular grid with 2 mm spacing within the tissue using a 1.5-MHz custom-made transducer (80 mm diameter and 60 mm focal length). During sonications, hyperechoic regions were visualized at the focus on B-mode and boiling histotripsy induced bubbles were also detected using color Doppler mode. Histological analysis showed lesions containing homogenized cell debris that is consistent with histotripsy induced mechanical ablation of glandular elements. Close to the edge of the lesion the regions of completely homogenized tissue were intermixed with regions of intact smooth muscle and collagen fibrils consistent with sparing of fibromuscular elements. In conclusion, these data represent the first successful application of boiling histotripsy in ex vivo human prostate tissue and suggest that mechanical prostate ablation is feasible. Further work is ongoing to evaluate a prototype preclinical transrectal device while optimizing parameters of the boiling histotripsy pulsing scheme.

Miscellaneous Tumors

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

Aerang Kim from Children's National Medical Center discussed MRgFUS for the ablation of relapsed or refractory pediatric solid tumors. Acute toxicities and late effects of current multi-modal therapy in pediatric cancer are substantial and the prognosis for recurrent/refractory sarcomas and solid tumors remain dismal. There is a need for precise and less toxic treatment options in pediatric cancers. MRgFUS has been studied in a variety of solid tumors in adults and for pain relief from bone metastases. The primary objective of this clinical trial was to determine the safety and feasibility of MRgFUS ablation in children, adolescents, and young adults with relapsed/refractory solid tumors. Secondary objectives include the evaluation of changes in functional imaging, quality of life, and immune markers in children treated with MRgFUS. Patient imaging and eligibility were reviewed by a multidisciplinary MRgFUS team. Patients underwent MRgFUS treatment of selected lesion(s) under general anesthesia. Patients were followed for 14 days post-treatment and monitored for adverse events. The first six patients

(median age 14 years (range 4-21)) enrolled on the trial were evaluated. All related toxicities were mild with transient pain and skin burn being the most common and all were transient and reversible. Two patients underwent a second MR-HIFU treatment of another target lesion, and one patient underwent a second MR-HIFU of the same incompletely treated target lesion. In conclusion, MRgFUS ablation of solid tumors in children, adolescents, and young adults appears to be safe and feasible. Response and changes in quality of life, patient reported outcomes, and immune markers' analyses are underway. The study was expanded to enroll six more patients for additional safety and feasibility experience and outcomes. The trial is open to enrollment and accrual is ongoing.

Edwin Heijman from Philips Research Germany spoke about a case presentation of volumetric hyperthermia of soft tissue sarcoma using MRgFUS. A patient (59-year-old male) with dedifferentiated liposarcoma of the right spermatic cord infiltrating the femoral vein next to the pelvic bone and bladder inducing pain underwent MRgFUS. Metastases were found in the psoas major muscle and lungs. The patient received a combination of olaratumab (before) and doxorubicin (after) MRgFUS every 3 weeks. The MRgFUS hyperthermia therapy was offered as a treatment option to alleviate pain and support the chemotherapy. Seven treatment cells with 10 mm diameter each were spatially arranged within the tumor to yield a round treatment cell cluster with an overall diameter of 3.2 cm. Sonications were performed at an acoustic frequency of 1.0 MHz with a target temperature set to 42.5°C. A newly developed Hyperthermia Manual Control application tool was implemented in the hyperthermia build of the Sonalleve therapy console software allowing the physician to manually pause sonications or adjust sonication power during the treatment. Over the sessions, it became more difficult to maintain the temperatures in the tumor even after increasing the acoustic power. The patient did not receive additional analgesia and tolerated the periods of sonication very well. No adverse events or discomfort were reported. In conclusion, the MRgFUS induced hyperthermia therapy was successful and safe.

Pavel Yarmolenko from Children's National Medical Center presented on the targetability of canine soft tissue sarcomas with MRgFUS. Soft tissues sarcomas are mesenchymal cell tumors in both humans and dogs. In canines, they account for 15% of all skin tumors and 7% of all subcutaneous tumors. The purpose of this retrospective study was to determine the feasibility of using MRgFUS to treat soft tissue sarcoma in dogs. A retrospective search of medical records of dogs admitted to the Virginia-Maryland College of Veterinary Medicine was performed. In the five-year period from January 1, 2012 to December 31, 2016, 53 dogs were found with a diagnosis of sarcoma and available cross-sectional imaging of the tumor (MRI or CT). Targetability of these with a clinical MRgFUS platform (Philips Sonalleve V2) was analyzed and distances to critical structures (vessels, nerve, bone, bowel) were measured. Tumor tissue (in bone as well as in soft tissue) was considered targetable unless the ultrasound path was completely obstructed by bone or gas, or the target was within the spinal cord or less than 1 cm from the margin of the spinal cord. The majority of tumors (81%) examined were targetable with the defined criteria. The majority of truncal and axillary tumors were more than 50% targetable (88.9%) and all extremity tumors were considered targetable (100%). The highest proportion of non-targetable tumors (36%) were found in the head and spine. In conclusion, the majority of canine soft tissue sarcomas were targetable, and therefore MRgFUS is a potential therapeutic modality for treatment. Furthermore, this veterinary application is a possible model for the treatment of naturally-occurring soft tissue sarcomas in humans.

Ashish Ranjan from Oklahoma State University discussed a case series of the treatment of solid tumors and non-healing wounds in veterinary patients with MRgFUS. The objective of this ongoing veterinary clinical trial is to determine the potential of FUS in treating companion animals (client-owned dogs) with spontaneous oral cancers and infectious wounds. The non-healing wounds caused by hard-to-treat biofilm-forming bacteria in canine patients replicate the infection profile in humans. Four cases were presented. Case #1 was a 9-year-old Shetland Sheepdog, castrated male with a plasmacytoma mass on the lower right lip margin at the level of the canine/premolars that extended into the gum margin. Twenty-one days after treatment, the tumor mass disappeared. Histopathology from the treated area found an absence of tumor cells and an increase in immune cells, suggesting that FUS may have

promoted immunomodulation. Case # 2 was a 10-year-old, male, castrated Border Collie with a firm acanthomatous ameloblastoma mass on the mandible. The patient was treated with a 3 to 5-minute ablative procedure that covered 60% of the tumor volume. The tumor mass fell off a few days after treatment. After 3 weeks, no tumor mass was present. Case # 3 was an 8-year-old spayed female Yorkshire Terrier with a large, raised, red, hairless cutaneous mast cell mass on the left upper lip extending into the lateral margin of the nostril. The patient was treated with a 3 to 5-minute ablative procedure that covered 50% of the tumor volume. After 3 weeks, there was a reduction in tumor volume. Additional studies to determine the characteristics of tumor infiltrating immune cells in the oral biopsy masses and the efficacy of FUS to augment antimicrobial efficacy in pet patients are currently ongoing. Additionally, case #4 was a canine patient with a non-healing infected wound in the elbow region. The patient was treated with enrofloxacin solution 5 minutes prior to FUS, and the wound region was heated for 1 to 3 minutes to a temperature of 45°C. Bacterial culture performed in the non-healing wound patient to determine the presence of biofilm pathogens indicated the absence of infection at the end of the first treatment. In conclusion, early clinical data suggests promising tumor remission and infection clearance following FUS treatment in veterinary patients.

Ali Mohammadabadi from the University of Maryland presented on pFUS to enhance the delivery of therapeutic agents for the treatment of head and neck squamous cell cancer in a mouse model. Previous research demonstrated that pre-treatment with pFUS could enhance the effects of various therapeutic agents such as systemic administration of cortisone and local delivery of TNFα. This study investigated the use of pFUS to deliver cisplatin in order to lower the dose needed and the overall toxicity of the treatment. Tissue-penetrating particles coated with polyethylene glycol were used to deliver therapeutic agents. Preclinical mouse tumor models were used in these experiments. Cisplatin was administered systemically with and without nanoparticle coating. Pre-treatment with pFUS enhanced the delivery of nanoparticle-coated cisplatin by 30 to 40%, and did not enhance the delivery of free drug. Histology analysis showed a greater penetration of cisplatin into the tumor with pFUS pre-treatment and nanoparticle delivery. Future experiments will optimize the pFUS procedure. In summary, pFUS plus nanoparticles enhanced delivery of cisplatin in a mouse xenograft model.

Rajiv Chopra from UT Southwestern Medical Center discussed the treatment of Ewing's sarcoma by thermosensitive liposomal doxorubicin. Doxorubicin delivery using thermosensitive liposomes and MR-HIFU hyperthermia might enable enhanced local control in solid tumors without increasing cardiotoxicity. This study evaluated the tumor control achieved using the combination of thermally sensitive liposomal doxorubicin (ThermoDox) and MR-HIFU mild hyperthermia in a rodent pediatric tumor model (ES-1, human Ewing's sarcoma cell line). The tumor growth in rats treated with ThermoDox and MR-HIFU mild hyperthermia was measured and compared with controls. Nine days after tumor inoculation, the rats were treated with mild HIFU (42°C) for 30 minutes using a small animal MR-HIFU system (RK100, FUS Instruments) on a 3T MRI. ThermoDox (2.5 mg/kg, ThermoDox®, Celsion) was infused over 5 minutes through the tail vein starting when the tumor temperature reached 41°C. Tumor volume was measured every 2 days after treatment using a 1T MRI for up to 2 months. To date, 1-month data are available. ThermoDox plus HIFU had a significant effect in controlling the tumor growth compared with the control group. In conclusion, cytotoxic doses of doxorubicin can be locally delivered to ES-1 tumors in rats using MR-HIFU mild hyperthermia and ThermoDox. The combined strategy showed a reliable controlling effect on the tumor growth.

Matthew Bucknor from the University of California at San Francisco presented on the role of technical parameters on the ablation volume of desmoid tumors with MRgFUS. MRgFUS devices and software for ablation of desmoid tumors were developed with technical parameters for the treatment of uterine fibroids, which can demonstrate very different responses to heating than desmoid tumors. The purpose of this study was to retrospectively review MRgFUS treatments of desmoid tumors to determine the technical treatment parameters that contributed most significantly to accumulation of the ablative thermal dose. Sonication data was retrospectively reviewed from all MRgFUS treatments performed in histologi-

cally confirmed desmoid tumors over a period of 18 months from December 2014 through July 2016. Recorded sonication parameters included transducer roll (degrees), transducer pitch (degrees), power (W), sonication duration (s), sonication energy (J), focal height (mm), average temperature (Celsius), sonication type (short, nominal, or elongated), and accumulated dose. A linear mixed effects model was then used to determine the relative effect of each parameter on accumulated dose. Thirteen desmoid tumor treatments were performed at our institution over 18 months in seven patients. In total, data from 946 individual sonications were reviewed. Multiple technical parameters had significant contributions including roll, power, duration, dose area, energy, and average temperature. Increases in these technical parameters were significantly associated with increases in accumulated dose volume. In conclusion, a variety of sonication parameters influence the ablation volume dose for each sonication during MRg-FUS of desmoid tumors.

Frank Wolfram from SRH Waldklinikum Gera discussed the development of MRgFUS techniques to treat lung cancer. Most lung cancer patients are unable to undergo surgery at diagnosis, but might benefit from minimally-invasive parenchyma-sparing interventions. In order to make MRgFUS available for these patients, a study to investigate the condition of one lung flooding (OLF) for ultrasound-guided-HIFU (USgHIFU) ablation of central lung tumors was carried out. This study was aimed to investigate patient groups with primary and secondary lung tumors under aspects of accessibility to OLF, tumor volumes, and locations to determine the patient population most likely to benefit. Patient files from consecutively diagnosed patients with primary lung cancer and lung metastasis were included. Accessibility to OLF was determined by the inclusion criteria for One Lung Ventilation. The tumor diameter, total tumor volume, number of nodules, and depth of location were extracted from radiological images. In the lung cancer group, 55.5% of patients were accessible to OLF, as were 67.5% of the lung metastasis group. Advanced chronic obstructive lung disease (COPD) caused the majority of the exclusions. All patients under the age of 50 showed no limitations to OLF. Increasing age had a significant correlation with inaccessibility to OLF. The mean tumor volume in the metastasis group was significantly lower compared with the lung cancer group. In summary, OLF was accessible to the majority of patients analyzed in this study. COPD was the main reason for exclusion.

Joan Vidal-Jove from Hospital University Mutua Terrassa presented on metastatic lung tumor treatment with HIFU. A case study in one patient that underwent USgHIFU was discussed. The patient was a 44-year-old male with a synovial sarcoma on the right thigh that metastasized to the right and left lung. The treatment objectives were to reduce the tumor bulk and generate an immune response. USgHIFU was used to treat the tumor. No complications occurred during the procedure. There was a small amount of tissue edema, and the patient was discharged the following day. Four days after the procedure, hemoptysis occurred with no systemic consequences. In conclusion, USgHIFU was feasible in a metastatic lung tumor. Further research on this procedure for lung cancer will be investigated.

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Breast

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

Patrick Dillon from the University of Virginia discussed FUS therapy combined with pembrolizumab for the treatment of metastatic breast cancer. Pembrolizumab is a PD-1 targeted antibody used in the treatment of multiple solid tumors to augment T cell activation. It is hypothesized that the combination of FUS with a PD-1 inhibitor will result in T cell infiltration into breast tumors as well as a systemic immune response. In this pilot study, pembrolizumab was combined with FUS and several outcomes were assessed. There was a biopsy before, after, and 10 weeks post-FUS to examine tumor tissue for CD8+ and CD4+ T cells, MDSC's, T-regulatory cells, and cytokine responses. The study design was randomized so that patients received either pembrolizumab 14 days before or 7 days after a single time

FUS partial tumor ablation. FUS was delivered by a Theraclion Echopulse device at 45W power, with a skin cooling device. Five patients, out of 12, have been treated to date. The median age was 62 and all patients had metastatic breast cancer and accessible primary tumors in breast or axilla. Increases in CD8+, FOXP3- tumor cells were observed in the peri-ablation zones. Increased numbers of PD-L1+ cells were also observed in peri-ablation zones. There have been no adverse safety signals. Observed side effects include ablation site pain, fatigue, nausea, and dyspnea. None of the patients experienced a clinical response as defined by RECIST criteria. In conclusion, FUS ablation in combination with pembrolizumab is safe and results in observable changes to the immune microenvironment in patients with metastatic breast cancer.

David Brenin from the University of Virginia presented on USgHIFU ablation of breast fibroadenoma. Fibroadenoma is a common benign breast mass that can cause pain, a palpable lump, and anxiety. This study evaluated the safety and feasibility of USgHIFU delivered by the Echopulse device (Theraclion) for treatment of breast fibroadenomas. This was a single-arm study to evaluate patient safety, cosmetic outcome, tumor response, and patient experience. The primary endpoints were palpability of lesion at 12 months, patient tolerability and satisfaction, and change in tumor volume. Twenty patients were enrolled, and 18 patients completed 12 months of follow up. There was a mean tumor volume reduction of 68.9% at 12 months. A mass was no longer palpable in 80% of patients, no patients reported pain, and cosmesis was rated by both patients and physicians as excellent in 100% of subjects. Fifty percent reported a painful mass prior to treatment, and no patients reported a painful mass at 12 months. No serious adverse events occurred. All adverse events were grade 1 or 2; no burns, damage to adjacent structures, or other toxicities were observed. In conclusion, USgHIFU is an effective, safe, and well-tolerated treatment for breast fibroadenomas resulting in minimal toxicity. Based on these results, a larger multicenter clinical trial is currently open to accrual in both the United States and Europe.

Niloufar Saharkhiz from Columbia University discussed in vivo human breast tumor detection and differentiation using harmonic motion imaging. Harmonic motion imaging is a non-invasive ultrasound-based elasticity imaging technique that assesses viscoelastic properties of the underlying tissue based on displacements induced by a periodic ARF. The capability of harmonic motion imaging in mapping, characterization, and HIFU ablation monitoring of breast masses in post-surgical human specimens has been previously shown. The clinical application of HMI was investigated in this pilot study. The objective was to assess the potential of harmonic motion imaging as a complementary tool for in vivo human breast tumor detection and differentiation. The HMI system consisted of two confocally aligned transducers: a 4 MHz FUS transducer to generate the 25 Hz oscillating acoustic force, and a 7.8 MHz phased array imaging probe to track the induced tissue displacements. A 1-D point-by-point raster scan of the HMI setup with a step size of 2 mm was performed automatically with a robotic arm controlled by a PC workstation. Four patients have been scanned to date. Harmonic motion imaging displacement maps of 15×50 mm2 were reconstructed from peak-to-peak displacements amplitude. The localized radiation force was strong enough to generate detectable displacements in stiff tumors. Early data suggests that harmonic motion imaging displacement has the potential to differentiate benign and malignant tumors. In conclusion, the initial feasibility of a harmonic motion imaging clinical system for the detection and differentiation of in vivo human breast masses was demonstrated. Ongoing clinical studies will focus on the optimization of the current setup for real-time acquisition, potentially distinguishing masses from normal tissues, and characterizing different tumor types based on harmonic motion imaging displacements, as well as HIFU ablation application.

Gynecological

Several presentations highlighted the use of FUS for the treatment of uterine fibroids, adenomyosis, and endometriosis.

Inez Verpalen manipulation techniques. The clinical applicability of MRgFUS for uterine fibroids is often constrained by the limit in focal depth of the MRgFUS system or interposition of small bowel loops in the sonication path. The aim of this retrospective study was to decrease screening and failure rates and to describe a manipulation protocol for MRgFUS treatment of uterine fibroids. The manipulation protocol included three different techniques. 1) the BRB maneuver (sequential applications of urinary bladder filling, rectal filling, and urinary bladder emptying). If step 1 failed, step 2 or 3 was implemented depending on the position of the uterus. 2) Uterus axial or retroverted; the uterus was manually manipulated into anteflexion and the position of the uterus was fixated with a speculum. 3) Anteverted uterus; patients were positioned into the Trendelenburg position to move the small bowel out of the pelvis. Additionally, abdominal massage was performed on both sides of the lower abdomen with movements toward the upper abdomen. There were no complications or thermal injuries to the bowel or uterus from the manipulation. Our treatment failure rate due to the interposition of bowel loops decreased from 20% to 0%. The screening failure rate decreased from 53% to 28%. In conclusion, the manipulation protocol decreased screening and treatment failure rates.

Martijn Boomsma from Isala Hospital presented results from the Focused Ultrasound Myoma Outcome Study (FUMOS). The primary endpoint for this study was to measure long-term outcome data of MRgFUS for the treatment of uterine fibroids. This was a retrospective, single-center study of 140 patients with symptomatic uterine fibroids who underwent MRgFUS therapy. Patients were asked to complete a questionnaire that included symptom severity, quality of life, pregnancy outcomes, patient satisfaction, and requirement for additional treatments. There were 101 patients included in the analysis. The reintervention rate was 33.3%, excluding nonresponders and technical failures. Overtime the protocol changed and became more restrictive to limit the nonperfused volume to 50%. Analysis of these two subgroups suggests that restricting the nonperfused volume to 50% resulted in greater rates of retreatment. In conclusion, these preliminary results support the hypothesis that long-term reintervention rates after MRgFUS are comparable with other reimbursed uterine-sparing treatment options.

Shrinivas Desai from Jaslok Hospital and Research Center presented on the efficacy of MRgFUS treatment of uterine fibroids. The objective of this study was to evaluate the role of MRgFUS in the management of uterine fibroids in terms of clinical improvement in symptoms as suggested by a decrease in symptom severity score and a reduction in nonperfused volume. All patients had contrast MR pelvis, symptom severity score, nonperfused volume, and delayed adverse events assessed 6 months post-treatment. Patients with uterine fibroids showing enhancement on screening MRI were recruited for the study. 1221 symptomatic fibroids in 722 women were selected for inclusion. The reduction in mean symptom severity score before (26.22) and 6 months post-treatment (17.16) was statistically significant. The mean fibroid volume before treatment was 145.76 cm3, which significantly decreased after 6 months of follow up to 105.75 cm3. The perfused volume achieved after the procedure was 88.21%, which resulted in a reduction of fibroid volume at 6 months. Adverse events following treatment were minor. Leg pain was seen in 15% of patients immediately after treatment and 2% continued having mild leg pain after 6 months. Recurrence rate after 6 months was 1.66%. In conclusion, MRgFUS provides a statistically significant reduction in symptom severity index and fibroid volumes at 6 months of follow up. The adverse event profile is acceptable with major events occurring in a very small percentage of patients.

Shrinivas Desai from Jaslok Hospital and Research Center discussed the efficacy of MRgFUS in adenomyosis. The purpose of this study was to assess the efficacy of MRgFUS in treating adenomyosis through the evaluation of the nonperfused volume and symptom severity score. Ninety-four women with 115 significant symptomatic adenomyoses were treated. The majority of patients (74%) had a

significant reduction in symptom severity score following treatment. The volume of adenomyosis decreased after treatment. Additionally, there was a linear correlation between the symptom severity score and nonperfused volume, suggesting that as the nonperfused volume is increased, the adenomyosis volume decreased and the symptom severity score also decreased. In conclusion, MRgFUS is able to achieve nonperfused volume values that will result in clinically significant reductions in symptoms.

Daniel Kushner from Florida Atlantic University Charles E. Schmidt College of Medicine presented on MRgFUS treatments for uterine fibroids. The FDA relaxed the guidelines to perform MRgFUS in women who wish to preserve and enhance fertility in 2015, allowing for the treatment of younger women. The objective of this study was to evaluate the efficacy of MRgFUS treatment in this new patient population. Of ninety patients that received MRgFUS ablation of uterine fibroids from May 2016 to December 2017, 68 patients were interviewed by phone while 22 patients were unavailable for follow up. A multinomial logistic regression was created to determine the relationship among changes in symptoms and independent variables including nonperfused volume, average fibroid size, number of fibroids, and age at treatment. Overall, 36 (52.9%) of the 68 patients reported an improvement of symptoms, 17 (25%) reported no change in severity, and 15 (22.1%) reported worsening of symptoms. In the younger patients (under 35 years of age), 10 of the patients who reported worsening of their symptoms and one patient with no change in symptoms underwent alternative treatment (5 hysterectomies, 5 myomectomies, and one uterine artery embolization). An increasing nonperfused volume was associated with improved outcomes. There was no correlation between patient age and outcome. In conclusion, in this small patient population of varying ages, 52.9% of patients that received MRgFUS reported an overall improvement of their symptoms. A majority (75%) of patients with a post-procedure nonperfused volume less than 50% experienced worsening symptoms, but did not have a significantly higher number of fibroids compared to the other groups. Of the patients with worsening symptoms, 60% went on to have an alternative procedure.

Jae Young Lee from Seoul University National Hospital presented results from a clinical trial for uterine adenomyosis using a portable ultrasound-guided HIFU (USgHIFU) system. USgHIFU for the abdomen was developed (Alpinion) to create a compact and portable system. The device has a multichannel 256 phased array transducer. This was a preliminary trial to look at the efficacy and safety of the USgHIFU device. Nonperfused volume change, adenomyosis volume change, and other quality of life instruments were measured (N=66). The overall tumor volume decreased from 42.0% to 29.7%. The larger the nonperfused volume, the greater improvement observed in the dysmenorrhea improvement index. After 3 months of follow up, quality of life scores improved, and symptom severity scores decreased. Minor adverse events such as abdominal pain, back pain, or vaginal discharge were frequent, but transient and resolved without treatment. Two serious complications occurred; one patient experienced a third-degree skin burn due to the patient being too deeply sedated and one patient with leg tingling sensation that resolved within 3 months. In summary, the portable USgHIFU was effective for the treatment of adenomyosis. The treatment demonstrated safety, but careful monitoring during treatment is necessary.

Gil Dubernard from Hospices Civils de Lyon presented on transrectal HIFU as a focal therapy for rectal endometriosis. Focal One is a transrectal HIFU device, which is validated to treat prostate cancer. The aim of this pilot study was to assess the feasibility, safety, and clinical efficacy of Focal One in patients with posterior deep-invasive endometriosis with rectal involvement. The inclusion criteria were: patients older than 25 years old, without a plan for pregnancy in the next 3 months, who presented a single lesion with rectal invasion, and after hormonal therapy failure. The probe was inserted inside the rectum under spinal anesthesia. There were 9 patients treated in the initial cohort. There was a significant improvement in dysmenorrhea, spasms, constipation, false urges to defecate, posterior irradiation pain, and asthenia 1-month post-treatment. After 6 months there was a significant improvement in constipation and false urge to defecate. A second set of 12 patients with endometriotic lesions located exclusively in the lower and mid-rectum were also assessed. There was an improvement in posterior irradiation pain, false urges to defecate, and dysmenorrhea after 1-month post-treatment. These patients also had a significant improvement in quality of life scores. In conclusion, HIFU therapy for posterior deep-invasive

endometriosis can be considered feasible and safe. Further studies are required to confirm these preliminary results and also to optimize the selection criteria for treatment of rectal lesions with Focal One device.

Vikash Sinha from Florida Atlantic University Charles E. Schmidt College of Medicine discussed the implications of artifacts from myomectomy/C-section scars on MRI images for eligibility for MRgFUS treatment of uterine fibroids. One of the contraindications for MRgFUS of uterine fibroids includes MRI artifacts along the beam path. The aim of this study was to determine whether artifacts from prior uterine surgeries have a significant effect on MRgFUS treatment efficacy or safety. A retrospective analysis of 19 patients was carried out. A total of 36 fibroids were treated with an average volume of 103 cm3 (range 7- 478 cm3). There was no significant correlation with artifact severity and percent nonperfused volume, or with fibroid size and percent nonperfused volume. There were no adverse events in this patient population except for one case of endometritis that occurred months after the operation, and thus unlikely to be related to the MRgFUS treatments. A possible etiology of the artifact could be from a small electrical field formed by the residual carbon compounds from the dye (D and C Violet No. 2) in the sutures that leaked into the tissues. In conclusion, post-operative artifacts do not impede MRgFUS ablation. Patients with a history of prior uterine surgery deserve a treatment attempt with MRgFUS, even with MRI artifacts, as long as they are aware of the potential risks.

Musculoskeletal

Presentations highlighted the use of FUS for musculoskeletal applications including chronic wound healing, reducing back pain, and the treatment of osteoarthritis.

Hannah Zwiebel from Tufts University described her work evaluating human anatomy and candidacy for FUS ablation of the medial branch nerve (MBN) of the lumber spine in patients with facet-related back pain. The research group retrospectively evaluated 100 noncontrast lumbar CT scans to measure the depth from the skin to the MBN at L2-L5 bilaterally. Other measurements included the smallest width of the pedicle and the three dimensions of the transverse process. The team built a stepwise linear regression model to identify the strongest predictors of MBN depth with independent variables including age, gender, vertebral level, body mass index, and pedicle side. The study found that a FUS beam capable of 85 mm and 97 mm penetration would be adequate to treat 75% and 90% of the patient population, respectively.

Sin Yuin Yeo from Klinikum der Universitaet zu Koeln (Cologne, Germany) described a systematic investigation into the optimal ablation parameters and the effects of varying acoustic powers on facet joint ablation in the setting of lumbar facet joint osteoarthritis as a cause of low back pain. FUS has been demonstrated to alleviate pain in a preliminary study in patients with low back pain. Five pigs were treated with the Sonalleve system, followed for 7 days for treatment effects and complications (e.g., edema formation), and sacrificed for histological analysis, which revealed ablation of bone, bone marrow, and cartilage of a facet joint. Hemorrhages were observed within the ablated bone marrow, but there were no complications related to the treatments. In conclusion, FUS ablation was a safe and effective treatment of facet joints at high acoustic powers.

Viola Rieke from the University of California San Francisco described a study to longitudinally evaluate the safety and effectiveness of using FUS ablation for arthritis and other degenerative changes of the sacroiliac (SI) joint in a chronic swine model. Researchers treated five animals with the Insightec ExAblate 2000 system in a 3T scanner using two different energies (n = 3 with 700J, n=2 with 1000J) at 1.35 MHz frequency. The left side was treated, and the right side served as control. Animals were survived for 5 weeks of follow up. None of the animals showed signs of pain or impairment after the procedure. Histology showed efficacy of targeting. Analysis of the data is ongoing. In summary, FUS ablation for the treatment of degenerative nerves demonstrates efficacy on early histopathological findings.

Jude Jaraki from Florida Atlantic University College of Medicine described his work evaluating the human sacrum for potential FUS ablation of the lateral branches of the sacral nerves in patients with SI joint pain. The research team retrospectively evaluated and measured 50 CT scans of the sacrum, between S1 to S4 bilaterally. The average distance from the skin to the posterior border of the sacrum, the average curved length of the posterior border of the sacrum, sacral thickness, sacral height, sacral diameter, and other parameters were calculated. The group also created three-dimensional reconstructions of each sacrum and developed a predictive model of the perpendicular distance from the skin to the sacrum at the midpoint of the SI joint and the lateral aspect of the sacral foramen. To date, no clinical studies have published these types of in vivo measurements for the posterior sacrum.

Amanda Beserra from the University of Calgary described her work evaluating the feasibility of using FUS as an adjuvant treatment for the management of osteomyelitis in patients with diabetes. The research team developed virtual treatment planning software on the Sonalleve platform and evaluated potential targets based on their location and the surrounding structures within the ultrasound beam path. The group then calculated the percentage of cases that could be treated along with the percentage of the bone infection that could be targeted. The retrospective study concluded that FUS could potentially provide a noninvasive adjuvant to antibiotic therapy treatment for patients with osteomyelitis sites located in the extremities.

Julianna Simon from Pennsylvania State University described an in vitro rat tendon study using ultrasound-guided histotripsy to treat rotator cuff tears. The idea was to use histotripsy to create microdamage in the affected tendons, which are highly collagenous, to induce a healing response. The research team compared histological and mechanical results from histotripsy with a Verasonics system to conventional dry needling therapy. Preliminary results showed that histotripsy could disrupt tendon tissues.

Rebecca Lorsung from the National Institutes of Health described her work investigating the biological effects of acoustic radiation forces and endogenous cavitation on the skeletal tissue microenvironment with pFUS. Dr. Lorsung's research team measured the increase in prostaglandin E2 (PGE2) as an upregulator of the mesenchymal stromal cell homing therapeutic effect in kidney and muscle cells. When evaluating each of the FUS parameters, PGE2 proved to be correlated to PNP, frequency, intensity, and a calculated mechanical index. The researchers concluded that PGE2 is upregulated at a PNP below cavitation detection thresholds, and it is likely that acoustic radiation forces alone can increase PGE2 levels. Finally, PGE2 levels were better correlated to the mechanical index than to the acoustic radiation forces. Future studies will examine the effect of adding microbubbles to the pFUS studies.

Scott Burks from the National Institutes of Health described in vitro work to elucidate the bioeffects of low-intensity pulsed focused ultrasound (LIPUS) for therapy and the mechanical effects of pFUS on hamstring muscle cells. In an effort to develop an alternative to the painstaking process of proteomic analyses, the team used dynamic transcriptional profiling via RNA sequencing to observe changes in skeletal muscle gene expression after LIPUS or pFUS. When comparing the two modalities, the research team found that the majority of changes were unique to each mode of focused ultrasound. Pathway enrichment analyses showed the transcription factors that were different between the two modes (e.g., pFUS upregulated the FOXO autophagy pathway whereas LIPUS inhibited it). This type of analysis can assist clinicians with determining which mode to use for various indications. Dr. Burk showed examples of these implications for diseases such as muscular dystrophies, sarcopenia, diabetic myopathy, and x-linked myopathy.

Devante Horne from the University of California San Francisco described a preclinical in vitro study to investigate whether using LIPUS to mechanically stimulate intervertebral disk cells might be a safe and noninvasive alternative to intra-discal growth factor injections for treating painful lumbar spine conditions. The research team designed and fabricated a LIPUS exposimetry system that addressed previously found problems with nonuniform near-field exposure, beam reflections, and temperature elevation within the sample. The group then performed and validated the study, discovering that LIPUS induced upregulation in collagen synthesis in bovine annulus fibrosus cells with a magnitude similar to growth factor treatment.

Cardiovascular

Presentations highlighted the use of FUS for a variety of applications in the treatment of cardiovascular disease.

Michel Nuta from Theraclion presented initial results from the company's ongoing clinical trial to prove safety and efficacy for using the Echopulse FUS device to noninvasively treat chronic vein disease (e.g., varicose veins). He presented several examples of positive results at 3 months follow-up and noted that most of the cases were performed without anesthesia. The treatment was well tolerated, and no severe adverse events were observed. Although more cases and longer follow-up are needed, preliminary data are encouraging and show that FUS could be a credible alternative treatment in this field.

Jean-François Aubry presented Nesrine Barnat's work from Institut Langevin. In this study, the research team used extracorporeal FUS to induce vein shrinkage in a sheep model to study lumen narrowing after FUS exposure. The idea was to create a noninvasive treatment for venous insufficiency in the lower limbs. To study the exposure, the group treated six saphenous veins from three ewes with Theraclion's Echopulse device using a 3 MHz therapy transducer and real-time treatment monitoring and then analyzed ultrasound images, quantified lumen narrowing, and evaluated macroscopic changes induced by FUS. After 30 days, lumen narrowing was still present with a median reduction of 51% ± 20% and vein wall shrinking was visible at the excision along with whitening of the treated zone (i.e., collagen fiber aggregation). All veins exposed to FUS showed significant wall shrinkage with a diameter reduction of at least 50%, and the vein wall constriction persisted over time.

Jean-François Aubry presented Nesrine Barnat's work from Institut Langevin. The study employed several sonication strategies to evaluate the use of FUS to noninvasively occlude incompetent veins in an in vivo rabbit model of venous insufficiency. The research team used numerical simulations to identify sonication parameters for smaller than and greater than a 2 cm vein segment (larger diameter than previously tested) and then sonicated 29 veins in 15 rabbits using Theraclion's Echopulse device and a 3 MHz transducer. Vein occlusion was evaluated after a follow-up period of up to 19 days. Both the larger and smaller exposure parameters achieved rabbit vein occlusion with a high rate of success. The study demonstrated the feasibility of USgFUS to induce durable occlusion (3 weeks) of veins with a diameter greater or equal than 2 mm, without injection of additional products such as pro-inflammatory agents. This work was subsequently translated to the clinic by Theraclion, as presented above.

Sergio Vega from the Hospital for Sick Children described a proof-of-concept study to create an ex vivo porcine model of a coarctation of the aorta and then determine whether it was amenable to FUS treatment with boiling histotripsy. The research team was successful in creating the model of aortic coarctation, testing four adjacent sonications (900 W, 51 s, 20 pulses, 0.21% duty cycle) within each mass, and conducting post-treatment imaging and histologic analysis. The concept for the basic ex vivo porcine model for coarctation of the aorta was successful, was treatable with FUS, and encouraged the development of further studies.

Miscellaneous Indications

Presentations highlighted the potential use of FUS to treat various new indications including ablation of hematomas, optogenetics applications, and bone regeneration. Also described were a novel microbubble specifically designed for use with FUS and predictive algorithms to improve thermal ablation with FUS. Additionally, the development of a massive open online course (MOOC) on FUS therapy was described.

Tanya Khokhlova from Moscow State University described progress on ongoing work to develop boiling histotripsy for liquifying large symptomatic hematomas. The current project (1) correlated the size and shape of liquefied boiling histotripsy cavities with the focused ultrasound transducer's field dimensions and the number of delivered boiling histotripsy pulses, and (2) characterized the stiffness of two types of in vitro hematomas. The research group measured the shear modulus (stiffness) of all samples with a custom-built indentometer, treated large volume samples using three different sized and powered transducers, and analyzed the results. The boiling histotripsy cavity became saturated after delivering 30 pulses for all transducers. The shear modulus measurements indicated that the large hematomas were much softer than vascular clots and did not stiffen with retraction. The dimensions and shape of the boiling histotripsy cavities correlated with the focused ultrasound field structure and can be modeled.

Cyril Lafon from LabTAU, INSERM presented on the introduction of a MOOC on FUS therapy. As part of its designation as a Focused Ultrasound Foundation Center of Excellence, LabTAU developed a MOOC dedicated to (1) educating students, patients, clinicians, and scientists on the use of focused ultrasound for therapy, and (2) promoting FUS to the medical community and, more broadly, to the general public. Twelve presentations from world-recognized experts were recorded for the first year, including content from Florent Aptel, Alexandre Carpentier, Sébastien Crouzet, Lawrence Crum, Jeff Elias, Pejman Ghanouni, Gail ter Haar, Chrit Moonen, Franco Orsi, Bruno Quesson, Oleg Sapozhnikov, and Shin-ichiro Umemura. The topics will include clinical cases, mechanisms, bioeffects, imaging/monitoring modalities, and the technical aspects of FUS administration. Each presentation is followed by a questionnaire for assessing the clarity of the message and interacting with the community. The MOOC also has an online forum. It is free and located on the University of Lyon's educational platform (clarolineconnect.univ-lyon1.fr).

Gun Kim from the University of Illinois at Urbana-Champaign introduced the concept of sono-optogenetics, a novel technology that couples FUS with a mechanoluminescent hydrogel to generate localized photon flux. The research team developed the system and then conducted experiments to determine threshold activation pressure and distinguishable light (blue) in the luminescent hydrogel during FUS exposure. They determined that FUS has the capability to remotely trigger mechanoluminescence in PEG-based hydrogels, potentially benefitting in vivo optogenetics research.

Thierry Bettinger from Bracco described the company's recent work in creating a novel microbubble to combine with ultrasound for therapeutic use. Bracco optimized the physio-chemical and acoustic properties of the new product, currently called "BR38," and recently completed comprehensive preclinical and initial clinical evaluations. The lipid-based microbubble is under investigation for applications such as sono-thrombolysis and drug or gene delivery. Microbubbles currently used were designed for diagnostic applications and not specifically for FUS. Pharmacokinetically, BR38 demonstrated persistence in the blood circulation for several minutes. These microbubbles are still in research and development, but are being designed to use with therapeutic FUS.

Lukas Sebeke from University Clinic of Cologne (Germany) described a project to develop and demonstrate a model predictive control algorithm and custom software for FUS treatment planning and real-time treatment monitoring. In both phantom and preclinical experiments, the novel controller outperformed currently available technology. The model predictive control algorithm yielded more

narrow temperature distributions and smaller steady-state temperature offsets than an on-off control algorithm, which could lead to safer and shorter focused ultrasound treatments.

Rebecca Lorsung from the National Institutes of Health described her study investigating the role of pFUS in mechanically regulating calcium signaling and cyclooxygenase-2 expression for mesenchymal stem cell homing. After previously confirming the mechanisms for calcium influx in kidney and muscle cells, the group recently completed further studies to confirm the effect in breast cancer cells, melanoma cells, mesenchymal stem cells, and neurons. The kinetics and magnitude of the response varied across the mammalian cell types, which were sourced from both humans and mouse models.

Mario Fabiilli from the University of Michigan described his work using heat-activated, gene-switching cells plus focused ultrasound to control the growth of tissue in bone regeneration. Although conventional tissue engineering approaches rely on scaffold-based delivery of exogenous proteins, genes, or cells to stimulate regeneration via growth factor signaling, these approaches currently do not allow active control of crucial factors such as the dose, timing, or spatial localization of the delivered growth factor. Therefore, the Michigan team developed stable cell lines containing heat-activated and ligand-dependent gene switches, incorporated a hydroxyapatite/fibrin composite scaffold, and used FUS to spatiotemporally control transgene expression of several growth factors in these cells at various time points. After conducting experiments to determine the optimal parameters, the research team observed significant and pattern-specific transgene activation in the composite scaffolds after exposure to 2 minutes of continuous FUS at 200 W/cm^2.

Junjie Yao from Duke University described a calibration-free, novel imaging modality for measuring absolute temperature during FUS treatment. Photoacoustic tomography is a hybrid between optical excitation and ultrasound detection. The team used pulsed laser to excite the molecules in the tissue: when the molecules in the tissue were excited, the molecules emitted ultrasound waves, which were then detected and reconstructed by the device. Along with performing functional studies, the research team used this imaging technique to visualize dermal blood vessels and the entire abdominal cavity of a mouse. With its temperature monitoring capability based on photo memory effect, the research team found photoacoustic imaging to have scalable and sensitive capabilities that are similar to other imaging techniques in both phantom and in vivo measurements. Future studies are planned to use the technique in prostate tissue treatments.

Ki Joo Pahk from the Korea Institute of Science and Technology described a collaborative study to investigate the formation (e.g., size and shape) and dynamic behavior of the boiling vapor bubble created during boiling histotripsy. With the goal of using boiling histotripsy for tissue fractionation in soft tissue, the research team used optically transparent tissue-mimicking gel phantoms and a high-speed camera to study bubble dynamics. They then conducted in vivo liver tissue studies to gather numerical and experimental evidence on the appearance of rectified bubble growth in a viscoelastic medium while accounting for tissue elasticity. The asymmetry in the shockwaves and water vapor transport resulted in rectified bubble growth and tissue decellularization.

Advocacy Partnerships

In "What can advocacy organizations do for you?" Jessica Foley from the Focused Ultrasound Foundation described advocacy and trade organizations with which the Focused Ultrasound Foundation has formed partnerships to advance the field. Because new focused ultrasound ideas and applications must take a long and complicated path through multiple barriers and obstacles, including those needed for commercialization, to reach patients, the Focused Ultrasound Foundation is positioning itself at the nexus of the industry's ecosystem to more quickly and readily provide the assistance to advance the technology. Toward this goal, the Foundation has formed relationships with the Advanced Medical Technology Association (AdvaMed), The Medical Imaging Technology Alliance (MITA), the Medical Device Innovation Consortium (MDIC), the Consumer Technology Association (CTA), the Biotechnology Innovation Organization (Bio), and the Medical Device Manufacturers Association (MDMA). These organizations have resources to help focused ultrasound companies with regulatory approval, reimbursement, the economic value proposition, advocacy with physicians, patient awareness, and much more. Because these organizations have relationships with legislators, the FDA, CMS, specialty medical societies, and other stakeholders, the Focused Ultrasound Foundation is building connections to educate them about focused ultrasound and identify ways to partner to advance the field. Dr. Foley invited the audience to participate in these efforts. In response to a comment from the audience, she also mentioned that the Foundation is developing similar partnerships with patient advocacy organizations.

The Medical Imaging Technology Alliance (MITA) serves as the leading organization and collective voice of medical imaging equipment and radiopharmaceutical manufacturers, innovators, and product developers. Mark Carol from Sonacare Medical and Chair of MITA's focused ultrasound working group described the state of the field for focused ultrasound treatment of prostate tissue and showed how a potential payor cost savings of $7 billion and patient cost savings of $1 billion could occur over 5 years if focused ultrasound were used to treat appropriate patients who are currently receiving either radical prostatectomy or radiation therapy. MITA's goal is to work with all medical imaging stakeholders on matters of joint concern to the medical imaging industry to fulfill their mission of reducing regulatory barriers, establishing standards, and advocating for the industry. Due to the efforts of the Focused Ultrasound Foundation, MITA added focused ultrasound to their list of imaging-based technologies, formed a focused ultrasound working group, and has made plans to add a representative from the working group to MITA's Board of Directors. The goals of the MITA focused ultrasound working group are to (1) develop working relationships with the FDA, CMS, and private payors, (2) establish relationships with relevant professional societies, (3) improve focused ultrasound marketability and messaging as a cancer treatment, (4) develop and execute a public relations campaign to raise the profile of focused ultrasound, (5) organize and host a Capitol Hill briefing, and (6) develop a bipartisan team of Congressional champions. The working group communicates via monthly conference calls, biannual in-person meetings, a bi-weekly newsletter, and through social media. Besides its working groups, MITA uses a committee structure to achieve objectives in several critical areas (e.g., reimbursement, coverage, and government relations). Dr. Carol invited anyone who is interested to join MITA and answered audience questions about self-insured companies, the Veteran's Administration, and the availability of grant money for innovative pain treatments that prevent opioid addiction.

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Thursday
October 25, 2018

Technology Gaps and Breakthroughs, Notable Treatment Successes and Failures

Presentations in this session highlighted recent technological breakthroughs that have helped to advance the field of focused ultrasound.

Jean-François Aubry from Institut Langevin in Paris, has employed the use of 3D printing to create custom acoustic lenses for more precisely focusing ultrasound in transcranial applications. This technique utilizes a customized acoustic lens to focus the ultrasound beam in place of a transducer array.

Vera Khokhlova from the University of Washington and Moscow State University, described novel simulation software that their team developed to assist scientists in designing, evaluating, and testing FUS transducers. The modeling package, called "HIFU Beam" is expected to be available by the end of 2018 at www.limu.msu.ru, and its simple user interface allows researchers to enter parameters from the transducer and the medium to predict wave forms, pressure, and intensity.

To show another recent advance in FUS technology, Dr. Khoklova presented her work to improve the design of high-power, high-density, multi-element transducer arrays that produce irregular sonication patterns. These novel transducers decrease interference with real-time imaging, decrease transducer size, and increase the ability to position the transducer in new ways.

Andreas Melzer, from the European Focused Ultrasound Charitable Society, presented an update from the FUSIMO project, which uses robotic-assisted focused ultrasound for motion tracking and beam steering in the liver. The group has begun the process of transforming the project into an ISO-approved clinical system and has developed sophisticated software that works with any FUS system to provide real-time imaging and real-time beam steering that follows its target according to the motion compensation algorithm. Preliminary data from the project's first in vivo experiment was presented.

Torsten Bove from TooSonix described the company's newly developed high-frequency FUS system for dermatology and small animal use. Besides being scaled for small animal use, the ONE-R device is designed for dermatology and dermato-oncology applications, where there are unmet needs for both benign and malignant conditions. The device can create lesions at varied depths and modulate temperature at the lesion site while applying heat very quickly or slowly over time. TooSonix is currently seeking partnerships for small animal experiments or cancer research.

Pejman Ghanouni from Stanford University presented three interesting cases from his and Alessandro Napoli's off-label use of FUS for osteoid osteoma and desmoid tumors. Together, the teams are learning the types of lesions that can, and cannot, be reached. Specifically, FUS cannot penetrate intact cortical bone to reach intermedullary lesions, but it can influence a lesion that is within the thick or dense cortical bone itself. A desmoid tumor located near an air-filled bowel produces unreliable thermometry readings, which can lead to damage or swelling in tissue beyond the intended field of treatment. In these cases, the location of the lesion can disqualify a patient for FUS treatment. Patient size and reduced range of motion also have the potential to disqualify a patient for treatment, but creative positioning and a thick gel pad for coupling allowed a heterogenous tumor to absorb enough energy for a successful treatment, essentially extending the focal depth of the system.

Panel Discussion: How to Forge Collaborations with the FDA

Panel Moderator: M. Myers
Panelists: T. Morrison, X. Zheng, B. Blumenkopf, G. Clement, and J. Tao

Tina Morrison described the FDA's recent cultural changes, renewed mission, and regulatory science program that will allow the agency to provide US patients with first-in-the-world access to high-quality, safe, and effective medical devices. The FDA realigned their strategic priorities and instituted new programs and initiatives to achieve measurable outcomes in specific areas. For example, the Center for Devices and Radiological Health (CDRH) has implemented flexible regulatory paradigms across the total product life cycle that have resulted in a four-fold increase in the number of novel device approvals and greater than 90% reduction in time to full investigational device exemption (IDE) approval. The center's defined strategies also include instituting early feasibility studies, allowing staged approvals, improving engagement, and building collaborative communities with all stakeholders. The FDA's ultimate goal is incentivizing manufacturers t o bring their devices to the US market first, or in parallel with other major markets. The CDRH's Office of Science and Engineering Laboratories (OSEL) works with the regulatory science committee to establish research priorities and then tasks their more than 130 scientists with conducting research across a broad spectrum of device science, including diagnostic and therapeutic ultrasound. OSEL's ultrasonics laboratory currently has five different areas of focus for various technologies and methodologies in the ultrasound device spectrum. Its scientists also collaborate with academic centers, professional societies, and industry.

Jim Tao described Insightec's 19 years of experience in collaborating with the FDA to achieve three premarket approvals (PMAs), approximately 40 PMA supplements, and more than one hundred IDEs. Communication is the key to successful interaction, and the FDA offers several unique opportunities to manufacturers including educational seminars, webinars, panels, an interactive and informative Q-submission process, and published guidelines. The informal and formal communication channels work well to navigate what can be a complicated process, and companies are wise to develop ongoing internal regulatory expertise within their teams.

The panel discussed the following topics

1. **How does the FDA approval process work for combination devices (i.e., a drug plus a delivery device)?**
   The FDA's new Office of Combination Products decides whether the Center for Drug Evaluation and Research (CDER) or (CDRH) takes the lead on reviewing a combination submission; however these centers all work together to review each combination submission, whether it is an investigational new drug (IND) or IDE application. It is not necessary to use both the IND and IDE forms. Investigators should choose one or the other. IDE is used for an existing drug that is delivered with a new device. In the past, CDER has taken the lead for the use of microbubbles. The interaction between the FDA and researchers is a highly collaborative and rigorous process that can be time consuming but effective for developing a protocol.

2. **What can be done to shorten the time period between FDA approval and reimbursement**
   Invite the Centers for Medicare and Medicaid Services (CMS) to join the discussion during the development of the protocol. Because insurers seek proof that a novel therapeutic is better than what currently exists, researchers could also consider conducting a superiority trial rather than a noninferiority trial.

3. **What should companies or researchers who are conducting clinical trials outside of the US do regarding the FDA?**
   Submit the protocol to the FDA for review and comment before initiating the study. This could increase the likelihood of the FDA accepting data from the international study on any subsequent US application.

4. **How can the FUS community work together to prepare for submitting applications of novel mechanisms (e.g., histotripsy, BBB opening, or neuromodulation) to the FDA? What types of preclinical studies are required for these new mechanisms? Can the OSEL group speak to the development of standards for new FUS mechanisms?**
   OSEL is the face of the FDA for ultrasound, and industry representatives are encouraged to contact OSEL staff to learn what they deem to be important to the approval process. OSEL is open to collaborating with academia and the FUS community, especially in attending workshops and symposia that help motivate or inform their own research: identifying and solving challenges together assists in the overall collaborative effort, and FUS is a new area that has not yet amassed a volume of historical data or experience. OSEL is learning along with the community while assisting in developing both standards and useful tools for research, including FUS simulation software and tissue-mimicking phantoms. FDA representatives appreciate participating in focus sessions at conferences where attendees create lists of issues to overcome and clinical questions that need to be addressed. Preclinical testing can often be indication dependent.

5. **What is the right timing for approaching the FDA with a project?**
   The best timing is as early as possible after a device has been designed. Developers can request an informational meeting to introduce a concept or technology to the FDA without binding feedback from either party. This keeps FDA from being in the dark about emerging technology and allows their scientists to learn and keep pace along the way rather than catching up on several years of research. The key components for the FDA to understand are: 1) the device concept or design, 2) the target patient population, and 3) the risks of the device. These factors allow the agency to evaluate risk mitigation for safety and efficacy. Panelists also encouraged the group to bring scientific questions to the scientific team and regulatory questions to the review team.

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Path to Regulatory Approval

Laurie Clarke from Greenleaf Health described how the FDA device classification system is based on level of risk and how each of the three levels requires a different path to approval [e.g., 510(k), PMA, de novo]. Device classification regulations describe its indications, technological characteristics, class, and any applicable special controls. The 510(k) pathway for premarket notification is the most common path used for medical device approval. It requires proof of substantial equivalence to a predicate device. The PMA pathway is the most rigorous route to approval, and it requires a comprehensive demonstration of the safety and effectiveness of the device based on clinical data for specific indications. The de novo pathway is used for novel low- to moderate-risk devices with no predicate device. It often requires submission of clinical data. Clinical data can be collected after the FDA approves an IDE application for a given device, and investigational devices cannot be promoted. Combination products combine drugs, devices, and/or biologics, and the primary mode of action determines whether the therapeutic is assigned to CDER or CDRH.

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Path to Reimbursement

Stephanie Kennan from McGuire Woods Consulting described the three separate processes that lead to Medicare reimbursement: coding, payment level, and coverage. Coding is the language that the Centers for Medicare and Medicaid (CMS) and other payors use to define a medical procedure. A code can be based on where the procedure is performed and what type of product is used. Coding is not a political process; it is based on data and the support of the medical community. The payment

level determined by CMS can be set before coverage is granted. It depends on the type of device or service and includes an annual Medicare payment rule. CMS classifies similar devices and services into groups. It is important to educate CMS staff about the device or service to prevent placement into the wrong classification group. Manufacturers should meet with CMS staff after completing a cost analysis and be prepared to educate the staff and provide cost data for an appropriate payment level. CMS employs both career staff and political staff. After CMS sets the annual Medicare payment rule, there is a period for public comment, so it is best to meet with the political CMS staff before the payment rule becomes public to make them aware of any issues. Payment levels are not permanent; they are adjusted as claims data become available. It is important to educate facilities on how their claims affect future payment levels because CMS uses two years' worth of claim data to adjust payment levels. The two ways to obtain coverage are through a national (CMS in Baltimore) coverage decision or through local coverage decisions from each Medicare contractor (MAC) in the country. It is difficult to reverse a negative national coverage decision. Congress recently passed legislation to make this process more transparent. A commenter from the audience confirmed that correct billing is as important as billing at all. Ms. Kennan agreed and said that is important for the people who decide how much to charge at each treatment facility to understand the difference between research costs and commercial costs.

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Innovative FDA Programs for Accelerating Regulatory and Reimbursement Approvals

Charles Viviano from the FDA said that because accessing the FDA had been viewed as a confusing or frightening obstacle, CDRH has taken steps to improve customer service and to increase availability and interactions with sponsors (i.e., manufacturers) while they complete the process of providing the evidentiary requirements needed for regulatory approval. The FDA has recently become aware that gaining reimbursement has become a steeper challenge than obtaining regulatory approval. In fact, reimbursement has become the missing piece of the puzzle for gaining access to the market and widespread adoption of a new technology, especially for the patients who need new treatment options. Communication problems exist when the language used for regulatory approval is different from the language used for reimbursement.

FDA Commissioner Scott Gottlieb, M.D., has taken steps to accelerate and improve patient access to medical devices, including using their unique position and structured interaction format to work collaboratively to streamline the process to reimbursement. The FDA's Payor Communications Task Force (Email: CDRHPayorCommunications@fda.hhs.gov) is charged with facilitating earlier communication and encouraging voluntary interactions between device manufacturers and payors to potentially shorten the time between FDA approval or clearance and coverage decisions. However, this process does not mean parallel review and there are some negative aspects. Therefore, the FDA is now encouraging manufacturers to engage payors during the pre-submission process (Email: Parallel-Review@fda.hhs.gov) and to simultaneously seek both approvals in tandem. Dr. Viviano further described the CDRH pre-submission process and differentiated how the FDA and reimbursement processes differ.

The goal of the FDA's Private Payor Program is to allow clinical data to also serve as clinical evidence for reimbursement purposes. The program's voluntary, six-part process is completed during the pre-submission meeting and has several benefits (e.g., payors may encourage collection of certain types of data during the clinical study). Sponsors can also directly contact payors, and a list of payors who are participating in the program is available online.

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Role of Block Chain and Artificial Intelligence in FUS

Rick Hamilton from Optum, in discussion with Neal Kassell, spoke about the role of block chain and artificial intelligence in FUS and the role of the Foundation in this area. Block chain is a database that is available to all users that allows a history of all transactions over time. It is an 'append only' database, and in order to correct a previous transaction, a new entry is created. It was developed for bitcoin, but it is the underlying process that is the interesting piece. Block chain solved the electronic cash double spend problem in the absence of a central authority. It's a resilient database as all users have a copy of the database, and therefore one person or computer cannot take down the whole database. Block chain has three potential healthcare applications: managing and exchanging data (i.e. health records or sensor data), automating processes such as smart contracts (claims coordination, benefit coordination, and payment integrity), and tracking and tracing assets (lab specimens and pharmaceuticals). Currently, these are being tested in proof-of-concept trials. Applications specifically relevant to FUS relate to manufacturers, clinical trials (contract research organizations), protocol design, patient recruitment, regulatory approval, payer reimbursement, data analysis, and publication preparation.

Hamilton also discussed artificial intelligence, which is also known as machine learning. Machine learning is when systems do not need to be explicitly programmed for all inputs. Machine learning is not a homogenous term, and there are fundamentally different approaches. Some examples are unsupervised learning (finding patterns in data), supervised learning (facial recognition), and reinforcement learning (autonomous vehicles). Deep learning is the use of artificial neural networks and is the driving force behind machine learning. Each network is comprised of layers of 'neurons' and each successive layer makes broader generalizations about the data it encounters. The technological advances in gaming processors have created the possibility of performing deep learning better and faster. Additionally, the increase in available data and enhanced software capabilities for training networks has moved the field forward. Broadly, machine learning can help manage well-being, diagnose chronic disease, and pinpoint treatment options. Machine learning can be an advisory tool. One application for FUS is selecting patients most likely to benefit from treatment. Another option is treatment planning, dosing guidance, and control.

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Panel Discussion: Clinical Trials and Registries in the 21st Century

Panel Moderators: T. Meakem and J. Torner
Panelists: M. Burtnyk, M. Carol, K. Dimeo, M. Hull, J. Hwang, and J. McIlwain

Kathy Dimeo from KAI Research described KAI as a highly experienced contract research organization that provides global services to government, academia, and industry. The company has a strong and highly developed data management core and comprehensive experience across each therapeutic area. KAI assists their clients with clinical trial design and management for feasibility studies, pivotal studies, and post-market studies and registries. Ms. Dimeo shared the benefits and challenges for several types of research studies, including randomized clinical trials, clinical effectiveness research, adaptive and platform clinical trials, and registries. She further described considerations for creating a registry.

John McIlwain from Velos described the organization's customers, network, products, and enabling technologies. Velos is a software company that specializes in clinical research. They have experience in electronically integrating study sponsors with their research sites, many of which are conducting National Institutes of Health-funded studies. Regarding quality in research from a systems perspective, there are

three considerations: reuse, security and audit trail, and affordability. Reuse of a developed platform relies on data standardization and the use of common data elements. High-level security, a comprehensive audit trail, and appropriate permissions are essential for ensuring data protection and integrity. Because clinical trials are expensive, it is important to provide systems that are affordable in terms of cost and usability.

Joo Ha Hwang from Stanford University described the Focused Ultrasound Foundation's new international registry for the treatment of pancreatic cancer. After reviewing current statistics on this devastating disease, Dr. Hwang said that FUS has a role to play in treating pancreatic cancer for tumor control, pain control, improved survival, enhanced and targeted drug delivery, and immunotherapy. Five clinical FUS systems currently have the capability to administer pancreatic treatments, which have been ongoing since the 1990s in countries such as China. In fact, a meta-analysis of published clinical treatments for pancreatic cancer included data that showed a remarkable benefit for using FUS for pain palliation despite a possible trend toward publication bias. Because the field is likely not capturing all the available data, and several individual studies strongly support the use of FUS for treating pancreatic cancer, the Foundation is launching a registry called Focused Ultrasound for the Treatment of PAncReatic CanceR – InternAtional RegistrY (ARRAY) to capture prospective, common core patient data from multiple international sites. The data that are collected will be used to assess treatment parameters, patient population, safety, pain relief, tumor response, and survival. ARRAY will also be used to generate research hypotheses rather than as a regulatory registry.

The following comments were made during the remainder of the panel discussion:

Mark Carol from SonaCare Medical described the SonaCare prostate patient registry, which is housed in the United Kingdom, managed by a board of directors, and currently maintains two sets of data for patients in the US. The first data set contains information from all present and past patients treated with the SonaCare Sonablate device; the second data set includes information from patients who are being enrolled in an ongoing IRB-approved prospective study. General registry data are available to academic and non-academic researchers, and the REDCap (Research Electronic Data Capture)-based platform has registered approximately 2,000 patients in Europe and 400 patients in the US.

Matthew Hull from EDAP-TMS said his company is supporting a clinical registry for patients treated in the US with the Ablatherm robotic-assisted device for focal prostate ablation. The FoR-UsA (Focal Robotic Ultrasound Ablation) Registry is based at the University of Miami with additional enrollment sites at the Cleveland Clinic, Duke Medical Center, Houston Methodist, University of Southern California, and Weill Cornell Medical Center. Gaining physician involvement was important for launching the study, which is also stored on the REDCap platform.

Mathieu Burtnyk from Profound Medical said that, although his company has yet to achieve regulatory approval in the US, their two current devices (Sonalleve and TULSA-PRO) have gained the CE Mark in Europe and other countries. Profound is in the process of collecting prospective data for US regulatory review and is also considering developing a registry for future data collection. Dr. Burtnyk said that determining the use and potential outcomes for registry data for the prostate is critical due to the challenges that accompany their collection and maintenance (e.g., demonstrating effectiveness in a small sample size). The data that is collected in registries may not be the correct data for achieving reimbursement, convincing professional societies to recommend adopting a new technology, or recording patient preference information.

Tim Meakem from the Focused Ultrasound Foundation said that many stakeholders are interested in registry data; Dr. Burtnyk agreed, citing patients, physicians, manufacturers, professional societies, regulatory bodies, and payors. Dr. Hwang said that registry data support regulatory and payor outcomes but the chasm that exists between regulatory approval and payor reimbursement in the US prevents the enrollment of patients in the registry.

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Open Science

Emily White from the Focused Ultrasound Foundation described the Foundation's Open Science initiative. After explaining the concept as generally making it easier to publish or communicate scientific findings, Dr. White gave background information on the Foundation's efforts to establish an open science program based on recommendations made by Philip Bourne after the 2016 Symposium. Since that time, the Foundation's scientific team has held discussions with key stakeholders, attended several conferences on this topic, and established four organizational efforts to advance the program. The first effort is to encourage open access publishing by reimbursing up to $2,000.00 of any direct costs incurred from choosing this publication route. The second effort is to encourage researchers to deposit their final reports and manuscript drafts into a pre-print server such as arXiv, bioRxiv, PeerJ, CogPrints, or others. The third effort is to create a pre-print server owned by the Foundation (FocUS archive) but housed on the Center for Open Science's Open Science Framework platform. The Foundation is planning a future webinar on how to use the FocUS archive, and this will be part of the program's fourth effort: educating the community. Future plans include developing a repository or commons for data sharing. The Foundation strongly supports open science because doing so aligns with the mission of the Foundation and is in the best interest of the field.

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Panel Discussion: Training and Credentialing

Panel Moderators: S. Leblang and B. Wood
Panelists: M. Burtnyk, M. Carol, M. Hull, M. Nuta, and C. Viviano

Charles Viviano from the FDA presented information on physician training and credentialing for new medical devices, which is regulated by the Federal Food, Drug, and Cosmetic Act of 1938. The FDA must assure a reasonable level of safety and effectiveness, but there are no laws regarding how the training must be conducted or what it must include. The FDA is not allowed to regulate the practice of medicine; therefore, physician training and credentialing becomes a condition of approval for a Class III PMA or a special control for a Class II de novo device. For example, FDA implemented special controls for the de novo approval of HIFU for prostate ablation. During the pre-submission period, the sponsor typically proposes a training protocol, which is reviewed by the FDA and then agreed upon through an interactive process. Device labeling must reference any training requirements, and post-market studies can be used to assess the adequacy of training programs.

Mark Carol from SonaCare Medical described the Sonablate medical training and certification program, which includes (1) physician Sonablate training and certification, (2) physician post-training support, (3) medical facility staff training, and (4) office staff training and HIFU program development. This is the program that accompanied Sonablate's de novo approval, and it certifies that a user has been trained to operate the device but does not provide any type of credentialing. The physician training program is a four-stage process that begins with online training, moves into simulation training, and concludes with supervised use of the device with patients until the physician achieves competence. After certification, post-training live remote support is available, along with a patient registry database and an annual users meeting. The facility training and office staff training programs are also comprehensive, multi-step certification courses. Dr. Carol also recommends training a multi-disciplinary group of users for HIFU devices.

Amit Sokolov from Insightec described the training program for the Exablate MRgFUS system's commercial applications. Worldwide training is a challenge when international customers speak different languages and have varied training backgrounds. Considerations include who should be trained, who should do the training, the training of the trainer, the regulatory or legal implications for each country,

and the content of the training. Ultimately, Insightec's training program has been designed to reflect the cumulative experience acquired from worldwide use of Exablate for multiple applications. It includes the science behind the device, safe operation of the system, and utilization and optimization of system tools for safe and effective treatments. The Exablate training program is FDA approved. It begins with theoretical and hands on training, proceeds to a dry run and treatment coaching, then concludes with advanced training and evaluation for training completion. After training is complete, Insightec continues to provide remote support, updates, and periodic site visits. They also continue to accept feedback from each user on the training program and their use of the device.

Panelists made the following points during the remainder of the panel discussion:

Brad Wood from the National Institutes of Health said that it is important to identify the failure modes and risks for each new medical device, especially as they change over time. It is important to listen and gain feedback from the early investigators and adopters.

Matthew Hull from EDAP-TMS said that releasing their products in Europe prior to bringing them to the United States gave the company an advantage by having previously developed training programs. EDAP also solicits continuous in person and online user feedback. Furthermore, previously trained physicians have become proctors and evaluators for new physicians in the training program. EDAP also provides live support as a part of their post-training program. In response to a question, Mr. Hull said that the new European device regulations have not yet affected their physician training program, but the development and release of EDAP's second-generation HIFU device will require additional training and evaluation for the users who upgrade to the new system.

In response to a question about whether any type of physician can be trained to use a FUS system, Mark Carol from SonaCare Medical said that his company does not specify which specialties are allowed, or not allowed, to become Sonablate users, but 99.99% of their treating physicians are urologists. The FDA does not restrict the technology to any certain set of physician credentials. Dr. Carol said that the field of FUS is also ideally suited to interventional radiologists and radiation oncologists.

Mathieu Burtnyk from Profound Medical said that the MRgFUS systems require a multi-disciplinary team to conduct each treatment; the systems are not designed to be used by a single medical specialty. He asked the panel to consider whether the FUS community should develop credentialing standards to designate which medical specialties have the necessary background to enter FUS user training programs. Dr. Wood pointed out the credentialing and cost differences involved in physician training to use an ultrasound-guided system versus an MR-guided system.

In response to a question from the audience about whether medical societies might play a future role in physician training and credentialing for FUS continuing medical education, Dr. Wood said that the Focused Ultrasound Foundation may be able to serve in such a capacity. Dr. LeBlang agreed and added that the Foundation could possibly also assist in a physician credentialing program. The discussion concluded with panelists sharing several ideas for such an initiative.

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Obtaining Venture Capital

Ronny Ginor from Orbimed provided perspective from an active investor in a large private equity fund. To answer the question, "How do large funds think?" he explained that large (i.e., more than a billion dollars) multinational funds such as Orbimed, Deerfield, or Federated invest in early-stage companies based on the calculated internal rate of return, or dollars divided by time. The timing of the initial investment is critical, and it occurs when several important factors coalesce (i.e., basic science, clinical results, regulatory comfort, initial and consistent reimbursement that can be modeled, institutional investment interest, initial investments, and any initial returns). Mr. Ginor said that the Focused Ultrasound Foundation has consistently been knocking at the door asking whether the field has met enough of these factors, and the charts that the Foundation uses to track the progress of the field over the last 10 years are critical to investors. Large investments, such as Koch Disruptive Technology's recent investment in Insightec, indicate proper timing, and Mr. Ginor predicts that the FUS investment floodgates are poised to be opened in the next two to three years. Orbimed is excited about the investments that they will soon be making in the FUS space. He concluded by saying, "It's time to go for it;" and suggested that companies use the resources offered by the Focused Ultrasound Foundation.

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FUS Partners

Emily White from the Focused Ultrasound Foundation who is Managing Director of the FUS Partners Program, described how this new initiative was designed to systematize and formalize the Foundation's efforts and activities in connecting the focused ultrasound start-up community with investors around the world. The program's overarching goals are to (1) produce a quantum change in the rate of FUS adoption as a mainstream standard of care, (2) to grow and rationalize the device manufacturers segment of the community by providing capital and expertise and by facilitating the consolidation of the industry, and (3) to supplement the philanthropic funding stream of support for the Foundation. The Foundation brings its brand and reputation as a trusted and independent third party; its knowledge base, information, and data; its network and community based on strong stakeholder relationships; its team, board of directors, council, and donors; and its ability to connect, convene, and influence stakeholders to the FUS Partners program. The program offers several services to the FUS community, including maintaining an understanding of manufacturers' current and future strategies, such as potential financing and partnering needs; maintaining a list of investors interested in FUS (venture capital firms, family offices, Foundation donors, individuals, and operating companies) based on understanding their strategies and interests; connecting manufacturers and investors; connecting manufacturers with other manufacturers; connecting academic research laboratories with manufacturers for R&D collaboration and technology transfer; and assisting with due diligence. Companies can participate in FUS Partners by asking for help. There is no formal application process and the Foundation does not receive compensation for these services. FUS Partners does not make investments, provide investment advice, serve as a broker, or otherwise receive any compensation for services. Parties to successful transactions will be solicited for donations to the Foundation as a way to grow the field and de-risk its investment. Several members of the Foundation's Board of Directors provide oversight support to the program.

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Panel Discussion: Crystal Ball – FUS in Ten Years

Panel Moderator: N. Kassell
Panelists: R. Chopra, W. Gedroyc, P. Ghanouni, N. Sanghvi, and G. Woodworth

Wladyslaw Gedroyc said that in 10 years he would like to see five or six applications that are funded and utilized at multiple centers throughout the world for the benefit of patients on a day-to-day basis. There is progressive frustration that the clearly beneficial and effective treatments developed in the field of focused ultrasound remain on the fringes of medical practice in many ways for a variety of reasons.

Pejman Ghanouni said that he sees the field building off of the success with essential tremor. Using essential tremor as a model, prostate treatment should soon reach reimbursement. The volume of patients with essential tremor and intermediate-risk prostate cancer is steadily increasing. With regard to the transition from preclinical to clinical therapy, cancer immunomodulation will enter clinical medicine within 10 years, especially in breast cancer and prostate cancer. The footprint of FUS devices will change in the future and become tailored to each application, with some migrating away from MR guidance to ultrasound- or fluoro-guidance. Artificial intelligence will make treatment planning a smarter process thereby decreasing procedure time and increasing efficiency.

Graeme Woodworth said that similar to what thermography has done for measuring FUS ablation dosing, he sees further development of advanced techniques for both measuring the dosing of the other 17 FUS mechanisms and understanding the biology for each mode of ultrasound used. Measuring the effects and understanding the effects will help the field leverage the technology from a mechanism-informed perspective. The groups that are modeling diseases at a very high level would be good partners to develop the clinical translation platforms that will allow FUS scientists and device engineers to apply the findings to clinical trials.

Naren Sanghvi said that he has seen such progress in the development of ultrasound imaging, from the invention of echocardiography to the transmission of data from small villages via mobile telephones. He sees similar progress happening with FUS. Now that it is in the hands of clinicians, the technologies' capabilities will be more rapidly advanced, especially with more advanced built-in instrumentation. Immunotherapy, stem cell delivery, and pFUS are the mechanisms of the future.

Rajiv Chopra said that his technology perspective allows him to see the strength of FUS in its flexibility and in the capacity for the industry to design devices in any configuration. In 10 years, he sees the development of devices that are customized and optimized for specific applications. While the first-generation devices have shown proof-of-concept, future devices will be customized for speed and efficiency. In the future, he would like to see all of the technology be vendor agnostic and guidance agnostic, which would allow them to be moved from point-of-care to the operating suite to the radiology suite rather than housed in a single place. These changes will give FUS a permanent place in medicine.

Neal Kassell asked the panelists the following "rapid fire" questions:

- Today there are approximately 550 FUS treatment sites around the world compared to 10,000 sites for stereotactic radiosurgery treatment. How many will there be for FUS in 10 years? The panelists responses ranged from 2,500 to higher than 10,000 centers. Neal Kassell noted that as more of the world gains access to technology, the numbers should climb higher.
- Last year we estimated that 100,000 patients were treated with FUS around the world. How many will be treated 10 years from now? Panelists responses ranged from a million to more than a million. Naren Sanghvi said that the numbers should be similar to the number of babies who are

born having had ultrasound scans, and Graeme Woodworth said the number should be similar to the number of patients being treated with radiation therapy.

- What are the top three indications that will be treated with FUS in 10 years? Panelists responses included broad brain applications (especially movement disorders), multiple oncology applications (including liver, prostate, and pancreas), bone applications, and novel cardiovascular and infectious disease applications.
- What will be the top three mechanisms for FUS in 10 years? Panelists responses included drug delivery, immunotherapy/immunomodulation, thermal ablation, histotripsy, neuromodulation, and any mechanism that develops advanced control and feedback capabilities.
- Ten years ago, there were five FUS device manufacturers. Today there are 46. How many major manufacturers will there be 10 years from now? Panelists responses ranged from less than 50 to more than 400. The group said that it is difficult to predict, but there will be a plethora of approaches to deliver FUS and small companies are likely to be purchased by larger companies. Most agreed that there will be fewer companies with more products, and some believe that the largest global distribution companies will acquire the technology (e.g., Medtronic or Stryker). The growth of immunotherapy and changes in large pharmaceutical companies for drug delivery will also affect the FUS market.
- Any additional comments? Wladyslaw Gedroyc said that it is almost impossible to predict the field in 10 years, especially in light of where the field stood with brain applications 10 years ago when many scientists thought that it would be impossible to deliver FUS through the skull. Naren Sanghvi said FUS will play a role in the reduction of the cost of medical procedures. Neal Kassell agreed that our ability to predict is lacking when 10 years ago, a similar panel predicted that there would be 10 applications but there are already more than 100.

Closing Remarks

Neal Kassell thanked the participants for contributing to the success of the Symposium. He reflected on the successes of the symposium. In the past 10 years, there has been tremendous growth in the field of focused ultrasound. There is a greater understanding of FUS-related mechanisms, research into additional indications, growth in the number of manufacturers, the amount of financial investment, and the development of a collaborative environment for device approvals at regulatory agencies. There is a clear transition from a clinical trial environment to commercial applications. The Focused Ultrasound Foundation meetings will continue to focus on translational, clinical, and commercial research; more technical studies will be presented at International Symposium for Therapeutic Ultrasound (ISTU). Upcoming meetings include the Winter School, joint meeting of the ISTU European Symposium, and the 7th International Symposium on Focused Ultrasound in 2020.

Awards

Ferenc Jolesz Memorial Award

Seung-Schik Yoo, PhD, MBA

INSIGHTEC

The Ferenc Jolesz Memorial Award sponsor

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 Seung-Schik Yoo, PhD, MBA.

Dr. Yoo is an associate professor of Radiology at Harvard Medical School and a director of the Neuromodulation and Tissue Engineering Laboratory (NTEL) at Brigham and Women's Hospital. He also serves as a faculty member of Mind Brain Behavior at Harvard University.

His early pioneering work involved developing real-time functional MR-imaging to interpret the human mind and applying the technology to interface the brain function with machines and computers. Dr. Yoo's current research is in exploring a new mode of noninvasive brain stimulation modality utilizing focused ultrasound to control regional neural functions, including the activity of the brain. He is primarily interested in advancing the technique for various neurotherapeutics, but also likes to seek out new ways to link thoughts/brain processes between individuals.

"On behalf of all the splendid researchers that I have worked with, I am deeply honored to receive the recognition," says Yoo. "I would like to thank the inspirations and encouragement that I have received from my mentors, Drs. Tempany, Panych, and Jolesz. I would like to express my gratitude to Drs. Seltzer and Boland who provided us with a vibrant research environment, and thank the Foundation and INSIGHTEC for the award."

Dr. Yoo will be acknowledged during the Sunday evening Welcome 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. 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 noninvasive approach. He passed away suddenly in December 2014.

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

2018 Visionary Award

Narendra Sanghvi

Narendra Sanghvi

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

We are honored to present the award to Narendra (Naren) Sanghvi.

A focused ultrasound technology pioneer and entrepreneur, Mr. Sanghvi began working with focused ultrasound in the Fry brothers' laboratory at Indiana University School of Medicine more than 45 years ago. Following several years of work on a system to treat brain disorders, he began the pursuit of treating the prostate with focused ultrasound and formed a company, Focus Surgery Inc., now a part of SonaCare Medical. Currently, Mr. Sanghvi is the Chief Scientific Officer at SonaCare; he is also the inventor and developer of the company's Sonablate® HIFU device, which has treated approximately 20,000 patients with prostate cancer at more than 120 clinical sites worldwide.

"Today, diagnostic ultrasound is a major medical imaging modality due to its noninvasiveness and high temporal and spatial resolutions," says Mr. Sanghvi. "Similarly, highly focused ultrasound has the same attributes to be a significant player for therapeutic applications. Receiving this award from the Focused Ultrasound Foundation is a surprise and very exciting. The Foundation has played an important role in integrating the interests of scientific, medical, and commercial entities in this field, and it continues to provide timely synergism to make these novel therapeutic applications a reality."

Mr. Sanghvi will be acknowledged during the Symposium's Welcome Reception on Sunday, 21 October 2018, where he will briefly share his journey in focused ultrasound and vision of the future.

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 6th 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. One of the 2018 Young Investigator Awards is sponsored by Bracco Suisse SA.

Twelve Young Investigators are participating in the 6th 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 room. On Tuesday, 23 October 2018, during the poster session and reception, they will have an opportunity to showcase and present their work to the larger focused ultrasound community.

Pavlos Anastasiadis, PhD

Awarded for: Towards a model of FUS-mediated blood-brain barrier disruption in non-enhancing, glioma-invaded brain regions for testing improvements in therapeutic delivery [YI-7/P-YI-7]

Pavlos Anastasiadis joined the Translational Focused Ultrasound Research Laboratory in the Department of Diagnostic Radiology and Nuclear Medicine at the University of Maryland School of Medicine in 2016. The lab, under the directorship of Victor Frenkel, PhD, is part of the Focused Ultrasound Foundation-Designated Center of Excellence at the University of Maryland School of Medicine. His research efforts make up a key component of the lab's mandate to develop focused ultrasound-based procedures. His projects include the use of MRgFUS for targeted delivery of therapeutics, cancer immunotherapy for the treatment of brain tumors, and the delivery of cellular-based therapies. He was previously a Fellow of the German Research Foundation, the Max Planck Foundation, and the Fraunhofer Foundation. Prior to moving to Maryland, he worked at the National Cancer Institute- Designated University of Hawaii Cancer Center. Currently, as an NIH T32 Cancer Biology Fellow, he is associated with the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center. His NIH T32 advisory committee is composed of Victor Frenkel, PhD, Graeme F. Woodworth, M.D., Joseph A. Frank, M.D., Eduardo Davila, PhD, and Jeffrey A. Winkles, PhD. Pavlos is a member of the American Association for Cancer Research, the American Society for Biochemistry and Molecular Biology, the International Society for Electrical Bioimpedance, the Acoustical Society of America, the International Society for Therapeutic Ultrasound and the German Society for Cell Biology.

BRACCO

Award sponsor

Kamyar Firouzi, PhD

Awarded for: Efficient transcranial ultrasound delivery via excitation of lamb waves [YI-5/P-YI-5]

Kamyar Firouzi received his MS degree in mechanical engineering from University College London (UCL) in 2010 and a PhD degree in mechanical engineering from Stanford University in 2016. For his doctoral dissertation, he focused on the localization of objects in chaotic and reverberant enclosures, based on which he developeda lamb-wave multitouch ultrasonic touchscreen system. He was a Research Assistant with UCL from 2010 to 2011, where he developed a predictive computational tool for evaluation of photoacoustic imaging techniques for detection of brain tumors. He has worked on numerous problems in ultrasound/MEMS technologies, including modeling and design of ultrasonic transducers, photoacoustics, microbubbles, wave propagation, and numerical methods. His current research interests include transcranial ultrasound, ultrasound neuromodulation, ultrasonic flow-measurement, and ultrasound signal processing and inverse problems.

Marc N. Gallay, MD

Awarded for: MRgFUS in chronic therapy-resistant Parkinson's disease [YI-1/P-YI-1]

Marc Gallay currently works as a neurosurgeon at the Center for Focused Ultrasound Neurosurgery Sonimodul, Switzerland, led by neurosurgeon Daniel Jeanmonod. He received his medical degree at the University of Zurich in 2008. His doctoral dissertation, "Human cerebello- and pallidothalamic tracts: Stereotactic localization, interindividual variability and MR correlations," was obtained in 2009 at the University Hospital Zürich under the supervision of Dr. Anne Morel and Prof. Daniel Jeanmonod. There, he further studied the monkey and human insular cortex as a postdoc fellow before training in neurosurgery at the Kantonsspital St.Gallen and at the University Hospital Geneva. He completed his neurosurgical training in 2015.

Pooja Gaur, PhD

Awarded for: Histological study of focused ultrasound neuromodulation and MR-ARFI in sheep [YI-4/P-YI-4]

Pooja Gaur earned her BS in biomedical engineering at Johns Hopkins University and her PhD at Vanderbilt University under the mentorship of Dr. William Grissom. During her doctoral research, she developed MRI methods for measuring temperature changes in the body during focused ultrasound heating treatments. As a postdoctoral scholar working with Dr. Kim Butts Pauly at Stanford University, Dr. Gaur is investigating focused ultrasound through the skull and assessing tissue safety in the brain.

Tyler I. Gerhardson

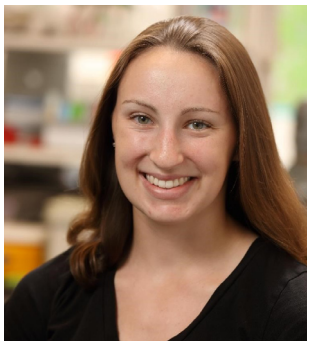
Awarded for: Histotripsy mediated immunomodulation in a mouse gl261 intracranial glioma model [YI-8/P-YI-8]

Tyler Gerhardson is a PhD candidate in the Department of Biomedical Engineering at the University of Michigan. He received a BS degree in biomedical engineering from Western New England University in 2015 and an MS Degree in biomedical engineering from the University of Michigan in 2017. Selected honors include the Dean's Award for Academic Excellence and Biomedical Engineering Department Award for Outstanding Senior from Western New England University, a Scholarship and Fellowship from Tau Beta Pi, and a National Science Foundation Graduate Research Fellowship. Tyler's research interests include ultrasonic standing wave separators, ultrasound transducers, and focused ultrasound therapies.

Yekaterina Gilbo

Awarded for: Detecting T1-based signal reduction in focused ultrasound heating of bone using a 3D spiral ultra-short echo time sequence [P-YI-13]

Yekaterina Gilbo graduated from the University of Virginia (UVA) in 2017 with a BS in physics and is pursuing a PhD in biomedical engineering at UVA. She is currently working on a project in MRgFUS that uses the magnetization properties of bone to detect potentially harmful skull heating.



Catherine Gorick

Awarded for: Focused ultrasound-mediated transfection of cerebral vasculature independent of blood-brain barrier opening [YI-3/P-YI-3]

Catherine Gorick received an undergraduate degree in biological engineering from MIT in 2015. There, she was a four-year member of the varsity lightweight crew team, a member of the Tau Beta Pi engineering honor society, and a mentor for an undergraduate leadership development program. Now in her fourth year of a PhD program in biomedical engineering at the University of Virginia, Ms. Gorick is working in the Price Lab and her research focuses on developing a platform for ultrasound-mediated gene delivery to the cerebral vasculature for stroke applications.

Alexander S. Mathew

Awarded for: RNA sequencing of focused ultrasound-treated melanoma reveals that thermal ablation and hyperthermia elicit differential immunogenicity [YI-11/P-YI-11]

Alex Mathew received his BS in chemistry and BA in mathematics from the University of Virginia (UVA) where he is pursuing an MD/PhD at UVA in the Price Lab. Currently, he is integrating high throughput sequencing with systems biology approaches to uncover the mechanisms behind FUS immunomodulation to inform FUS and immunotherapy combination strategies.

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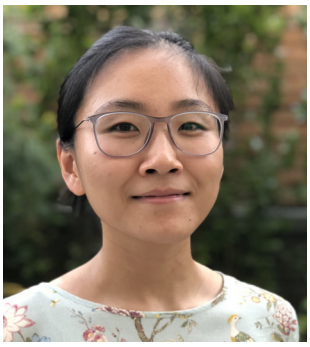

Ying Meng, MD

Awarded for: Blood-brain barrier opening in primary brain tumors: A demonstration of safety and feasibility with noninvasive MR-guided focused ultrasound [YI-6/P-YI-6

Ying Meng is a neurosurgery resident at the University of Toronto, researching neurologic applications of FUS under Dr. Nir Lipsman's supervision. Her interests and activities span from preclinical to clinical investigations involving neurological conditions such as movement disorders, traumatic brain injury, and neurodegenerative disorders.

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Daniele Mercatelli, PhD

Awarded for: Treatment of painful bone tumors using MR-guided focused ultrasound with conformal bone system [YI-12/P-YI-12]

Daniele Mercatelli is a postdoc research fellow active in the field of imaging and oncology at the Istituto Ortopedico Rizzoli. He holds a master's degree in cellular and molecular biology and a PhD in oncology and experimental pathology from Alma Mater Studiorum - University of Bologna. He has been working on the team headed by Dr. Alberto Bazzocchi since 2016, where he has been involved in managing and coordinating clinical trials investigating MRgFUS and its current applications in bone malignancies.
His main research interests involve the potential application of focused ultrasoundin the experimental treatment of osteoarthritis and benign bone and soft tissue tumors, broadened to wider aspects of cellular and molecular research.

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Francesco Sammartino, MD

Awarded for: Longitudinal analysis of lesion microstructural changes after focused ultrasound thalamotomy [YI-2/P-YI-2]

Francesco Sammartino received his MD from the University of Udine in 2008 and completed his neurosurgery residency at the University of Padova in 2015. In 2016, he completed a functional neurosurgery fellowship at the University of Toronto under the supervision of Prof. Andres Lozano. He is currently a research fellow at Ohio State University in the Center for Neuromodulation. Dr Sammartino's main inter est is neuroimaging applied to functional neurosurgery. During his fellowship in Toronto he chose to dedicate his research to personalizing the targeting and improving the outcomes after MRgFUS thalamotomy for essential tremor. He developed a methodology to help define the VIM region with the use of tractography, and he is currently involved in developing new methods to understand the mechanisms of tremor efficacy in the thalamus and the longitudinal microstructural changes associated with tissue ablation.

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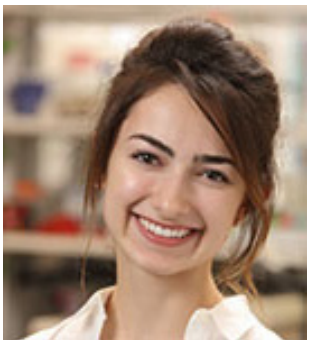


Natasha Sheybani

Awarded for: Leveraging MR image-guided focused ultrasound to potentiate immunotherapy for glioblastoma [YI-9/P-YI-9]

Developing synergy between immunotherapy and focused ultrasound ablation for metastatic breast cancer [YI-10/P-YI-10]

Natasha Sheybani is a fourth-year PhD Candidate and member of the Price Lab in the Department of Biomedical Engineering at the University of Virginia (UVA). Her graduate research centers on leveraging FUS to potentiate immunotherapy for primary and disseminated solid cancers. Natasha received her BS in biomedical engineering (with honors) from Virginia Commonwealth University. She is a recipient of the NSF Graduate Research Fellowship and UVA Robert R. Wagner Fellowship.

.....

FUS Foundation Internship Programs

Charles Steger Memorial Internship Program

The Focused Ultrasound Foundation's Summer Internship Program was established in 2012 with the goal of giving accomplished high school, undergraduate, and graduate students the opportunity to collaborate with leaders in the field on a variety of projects that address preclinical, clinical, and business challenges.

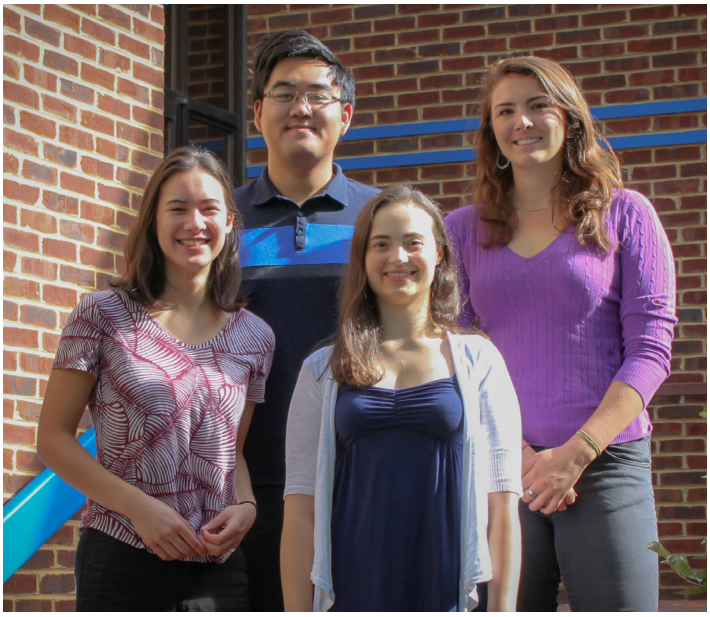
In May 2018, the Foundation's internship program–which encompasses both local and global interns—was named in memory of Board of Directors member Charles Steger, PhD. The Foundation's summer technical internships are generously funded by the Claude Moore Charitable Foundation.

Claude Moore
CHARITABLE FOUNDATION

The Claude Moore Summer Internship Program is part of the Charles Steger Focused Ultrasound Internship Program and is designed to foster interest in focused ultrasound technology among the next generation of researchers.

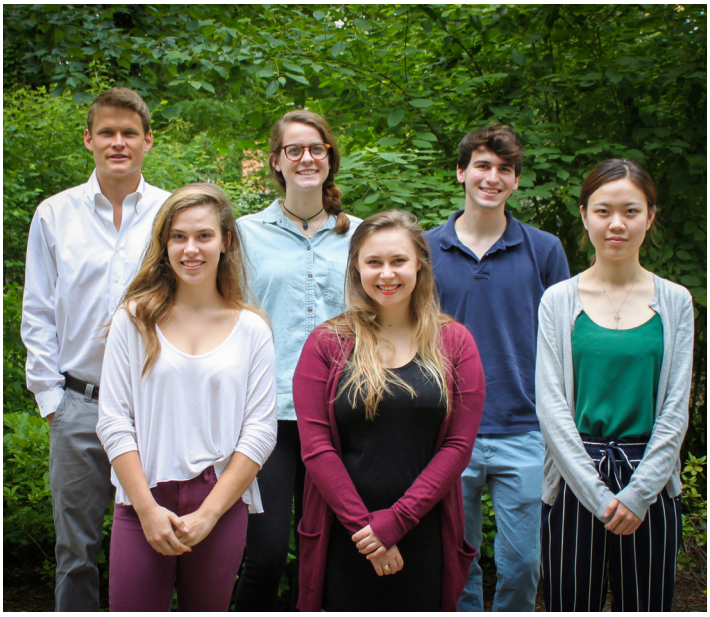
In the summer of 2017, the talented group of interns included four college students who worked on projects ranging from focused ultrasound patient registries to the use of 3D-printed lenses for transcranial focused ultrasound.

This summer, the Foundation welcomed seven students, including more nontechnical interns than in previous years. The group completed a wide variety of projects, working on everything from graphic design to the newly launched FUS Partners Program, to more technical projects like 3D-printed acoustic lenses and the use of software to automate and simplify research.



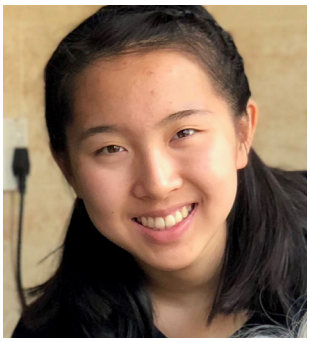
2017 Summer Interns

Left to right: Sara Hunter Chang, Derek Fang, Lindsey Abramson, Kassandra Tulenko



2018 Summer Interns

Left to right: George Brown, Lola Manning, Kate Snell, Marysia Serafin, Graham Keeley, Runmeng Zhai
Not pictured: Mailys Nier



Qingxi (Brooke) Ma

Receiving the highest peer-reviewed rating among submissions from the 2017 and 2018 FUSF Global Interns, Brooke Ma's abstract, entitled "Effects of focused ultrasound on delivery of intranasal GDNF DNA nanoparticles to the rat brain" earned her travel support to attend and present her work at the Symposium.

Global Internship Program

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

2017 Global Interns

Jessica Cahill
Georgia Institute of Technology
Atlanta, Georgia, United States
Mentor: Costas Arvanitis, PhD

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

Afton Holzer
University of Utah
Salt Lake City, Utah, United States
Mentor: Allison Payne, PhD

Yixuan Huang
Vanderbilt University
Nashville, Tennessee, United States
Mentor: Charles Caskey, PhD

Diana Kim
Columbia University
New York, New York, United States
Mentor: Elisa Konofagou, PhD

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

Roxanne Lahady
University of Paris
Paris, France
Mentor: Jean François Aubry, PhD

Jie Man Low
Institute of Cancer Research
London, United Kingdom
Mentor: Gail ter Haar, PhD

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

Alex Mueller
University of Utah
Salt Lake City, Utah, United States
Mentor: Dennis Parker, PhD

Andreas Mylonas
Cyprus University of Technology
Limassol, Cyprus
Mentor: Christakis Damianou, PhD

Shivani Patel
University of Maryland
College Park, Maryland, United States
Mentor: Rao Gullapalli, PhD, MBA

Andrey Polyanskiy
Moscow State University
Moscow, Russia
Mentor: Oleg Sapozhnikov, PhD

Lauren Puumala
Lakehead University
Thunder Bay, Ontario, Canada
Mentor: Laura Curiel, PhD

Tess Seip
SonaCare Medical
Charlotte, North Carolina,
United States
Mentor: Narendra Sanghvi

Bruno Souchu
University of Paris
Paris, France
Mentor: Jean François Aubry, PhD

Jinchao Wu
Stanford University
Stanford, California, United States
Mentor: Kim Butts Pauly, PhD

Yoko Zecchini
University College London
London, United Kingdom
Mentor: Wladyslaw Gedroyc, MBBS

2018 Global Interns

Neema Ahmadian
Virginia Polytechnic Institute and State University
Blacksburg, Virginia, United States
Mentor: Shima Shahab, PhD

Dylan Beam
Ohio State University
Columbus, Ohio, United States
Mentor: Vibhor Krishna, MBBS

Anastasia Bobina
Moscow State University
Moscow, Russia
Mentor: Oleg Sapozhnikov, PhD

Adam Canfield
Brigham and Women's Hospital
Boston, Massachusetts, United States
Mentor: Phillip Jason White, PhD

Megan Dearden
University of Utah
Salt Lake City, Utah, United States
Mentor: Doug Christensen, PhD

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

Maeghan Garrison
University of Virginia
School of Medicine
Charlottesville, Virginia, United States
Mentor: Wilson Miller, PhD

Tejas Karwa
Albert Einstein College of Medicine
Bronx, New York, United States
Mentor: Indranil Basu, PhD, MBA

Hohyun Lee
Georgia Institute of Technology
Atlanta, Georgia, United States
Mentor: Costas Arvanitis, PhD

Qingxi (Brooke) Ma
Northeastern University
Boston, Massachusetts, United States
Mentor: Barbara Waszczak, PhD

Craig Macsemchuk
University of Calgary
Calgary, Alberta, Canada
Mentor: Samuel Pichardo, PhD

Chris Margraf
University of Virginia
Charlottesville, Virginia, United States
Mentor: Timothy Bullock, PhD

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

Swadhin Nalubola
University of Maryland
Baltimore, Maryland, United States
Mentor: Rao Gullapalli, PhD, MBA

Somang Paeng
Seoul National University Hospital
Seoul, Korea
Mentor: Eun-Joo Park, PhD

Ekaterina Ponomarchuk
Moscow State University
Moscow, Russia
Mentor: Vera Khokhlova, PhD

Dia Shah
Albert Einstein College of Medicine
Bronx, New York, United States
Mentor: Indranil Basu, PhD, MBA

Alexander Simon
Virginia Polytechnic Institute and State University
Blacksburg, Virginia, United States
Mentor: Eli Vlaisavljevich, PhD

James Woznak
University of Virginia
Charlottesville, Virginia, United States
Mentor: Kevin Lee, PhD

Lin Zhang
Columbia University
New York, New York, United States
Mentor: Elisa Konofagou, PhD

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INSIGHTEC

www.insightec.com
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INSIGHTEC

INSIGHTEC® is a global medical technology innovator transforming patient lives through incisionless brain surgery with MR-guided focused ultrasound. With no incisions, there is no risk of infection, hospitalization is minimized or avoided altogether, and patients can quickly return to their lives.

The company's award-winning platform, Exablate NeuroTM, is being used to treat medication-refractory essential tremor. The result for many patients is immediate and durable tremor relief with minimal complications. Research for future brain applications is underway in partnership with leading academic and medical institutions. INSIGHTEC is headquartered in Haifa, Israel, and Miami, with offices in Dallas, Tokyo, and Shanghai.

Diamond Sponsor

Profound Medical

www.profoundmedical.com
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PROFOUND MEDICAL

Profound Medical is creating a therapeutics platform that provides the precision of real-time MRI combined with the safety and ablation power of both directional and focused ultrasound. We are commercializing TULSA-PRO® and SONALLEVE® which have CE marking for the ablation therapy of prostate, uterine fibroids, and bone metastases pain.

Gold Sponsor

Koch Disruptive Technologies

www.kochind.com

KOCH DISRUPTIVE TECHNOLOGIES

Koch Disruptive Technologies (KDT) invests in highly transformative growth companies that disrupt current market alternatives. KDT has a mutual benefit mindset, offering bespoke capital solutions and access to Koch Industries' global, multi-industry network..

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www.bracco.com

Bracco Imaging, part of the Bracco Group, is one of the world's leading companies in the diagnostic imaging business. Headquartered in Milan, Italy, it operates in more than 100 markets worldwide. Manufacturing activities are located in Italy, Switzerland, Japan, China, and Germany, while R&D activities are managed in three research centers located in Italy, Switzerland, and the U.S.

International Society for Therapeutic Ultrasound (ISTU)

www.istu.org
Advertisement: page 83
Not exhibiting

The International Society for Therapeutic Ultrasound (ISTU) is a nonprofit 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.

KAI Research

www.kai-research.com

KAI is a collaborative, "high-touch" clinical research company that conducts clinical trials, provides clinical research consultation, and implements data management and standardization services. For more than 30 years, we've helped commercial, academic, and federal clients bring innovative drug treatments and medical devices to market, including many years supporting focused ultrasound and related technologies.

Meggitt A/S

www.meggittferroperm.com

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.

Exhibitors and Supporters

Electronics & Innovation, Ltd.

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Electronics & Innovation Ltd (E&I) is a world leader in providing rugged and reliable RF power products. We want to work with you from research to production, benchtop to module. In addition to our standard product lines, we offer 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

The European Focused Ultrasound Charitable Society is a research and education organization serving as a philanthropic forum to establish research funding, sharing experiences, reviewing best practices, and promoting cooperation in the field of Focused Ultrasound for better patient treatment.

Focused Ultrasound Foundation (FUSF)

www.fusfoundation.org

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7th International Symposium: page 84
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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.

HistoSonics, Inc.

www.histosonics.com

Not exhibiting

HistoSonics is a venture-backed medical device company whose mission is to redefine cancer treatment with a noninvasive, highly precise, cost-effective method of tumor destruction called Robotically Assisted Sonic Therapy (RASTTM). The team at HistoSonics is currently developing a completely non-invasive robot that has the potential to deliver personalized treatments over a broad range of cancers in an outpatient setting. RASTTM is based on the science of histotripsy, a noninvasive ablation modality developed at the University of Michigan that uses the pressure created by focused sound energy to completely destroy tissue at a subcellular level.

Image Guided Therapy

www.imageguidedtherapy.com

Image Guided Therapy develops MR guided HIFU systemsfor preclinical research, based on phased array generators and transducer with up to 256 independent channels. IGT systems are used by renowned academic centers in diverse applications ranging from drug delivery to hyperthermia, ultrasound mediated blood- brain barrier opening, neurostimulation, and plain thermal ablation.

Exhibitors and Supporters continued

IMASONIC

www.imasonic.com

IMASONIC is a French independent, privately-owned company that develops and produces ultrasonic transducers and complete probes for health and safety applications. Since its creation in 1989, IMASONIC has been contributing to improving ultrasonic medical applications by designing and manufacturing transducers for therapeutic use, diagnosis, and monitoring. The company has 100 employees.

Korean Society for Therapeutic Ultrasound (KSTU)

www.kstu.or.kr
Exhibiting with ISTU

The Korean Society for Therapeutic Ultrasound (KSTU) was founded in 2014. Since inception there has been rapid membership growth with approximately 100 attendees at our annual meetings. This year, KSTU began an official exchange program with Japanese Society for Therapeutic Ultrasound (JSTU). We are looking to expand this program to other Asian societies for therapeutic ultrasound. KSTU is honored to host the symposium of the International Society for Therapeutic Ultrasound (ISTU) at Gyeongju, Korea, May 17–20, 2020.

Sonic Concepts, Inc.

www.sonicconcepts.com

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, Inc.

www.verasonics.com

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 and precise imaging and HIFU including targeting, guidance, treatment, and monitoring. Verasonics sells research systems and software, licenses its technology, and provides consulting services to academic and commercial investigators.

Partners

BIRD Foundation

www.birdf.com

The Israel-US Binational Industrial Research and Development (BIRD) Foundation's mission is to accelerate growth through strategic partnerships. The BIRD Foundation promotes and facilitates collaboration between US 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 percent of a joint project budget, the BIRD Foundation assists companies by identifying potential strategic partners in either Israel or the US 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 ReWalkTM, PoiseTM, Hockey IntelliGymTM; OnVuTM 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

The Michael J. Fox Foundation is dedicated to accelerating a cure for 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.

INTERNATIONAL SOCIETY FOR THERAPEUTIC ULTRASOUND

Registration is now open for the 19th Annual International Symposium for Therapeutic Ultrasound

Join scientists, engineers, clinicians and industry from around the world as we come together in Barcelona, Spain for the first joint meeting with the European Focused Ultrasound Charitable Society (EUFUS).

- Attend sessions covering topics ranging from Immunotherapy to Thermal Ablation, Modeling and Physics, and much more.
- Exchange ideas, collaborate, and envision novel applications of therapeutic ultrasound.
- Enjoy Barcelona's world-renowned art and architecture, and explore the beauty of the cosmopolitan capital of Spain's Catalonia region right on the Mediterranean Sea.

Save the dates now for the 20th Annual International Symposium for Therapeutic Ultrasound!

We look forward to your contribution to these exciting meetings.

Learn more and register today at ISTU.org

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, preclinical, 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 Dong-guk Paeng, PhD

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7th International Symposium on Focused Ultrasound

2020

Washington, DC area • November 2020

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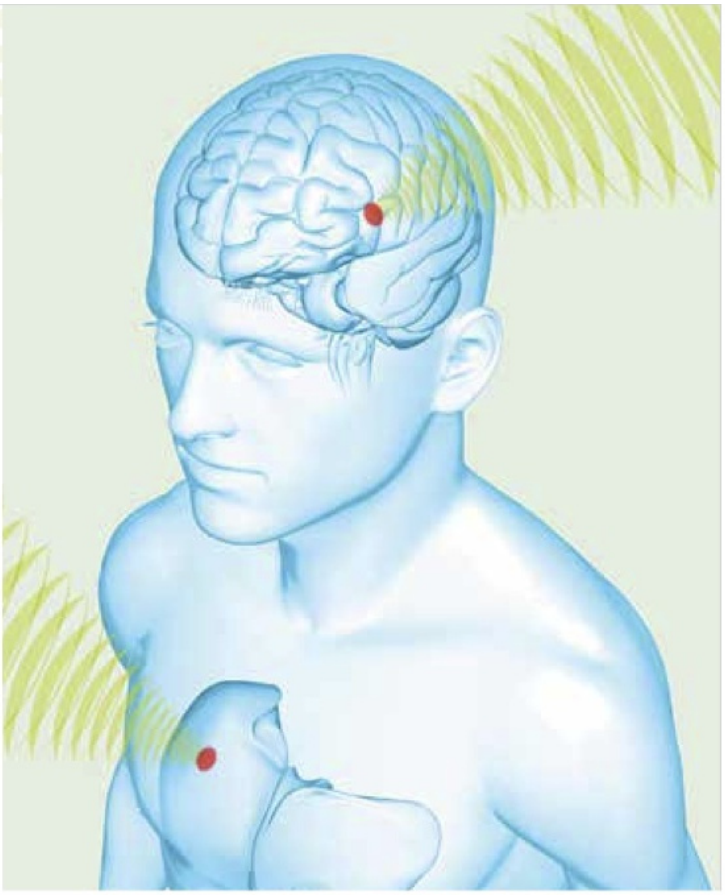

Thank you!

The Focused Ultrasound Foundation wishes to thank its exceptional Board of Directors and Council for their steadfast dedication to helping make focused ultrasound a clinical reality and improve the lives of millions of patients.

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The Focused Ultrasound Foundation was created to improve the lives of millions of patients by accelerating the development and adoption of focused ultrasound.

We leverage our independent status to drive progress by:

Funding Research

A key priority for the Foundation is funding translational studies, applying the growing body of knowledge to complex problems.

We fund internal research exploring technical aspects of treating the **brain** and **cancer immunotherapy**. Our **External Awards Program** also funds investigator-initiated clinical, preclinical and technical projects through a competitive peer-reviewed process.

Fostering Collaboration

We act as a global connector, hosting a variety of **workshops and biennial symposia** to stimulate innovation and increase awareness.

Overcoming Barriers

We **partner with industry** to help usher this technology through the regulatory and reimbursement processes and move the technology closer to patients.

www.fusfoundation.org

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