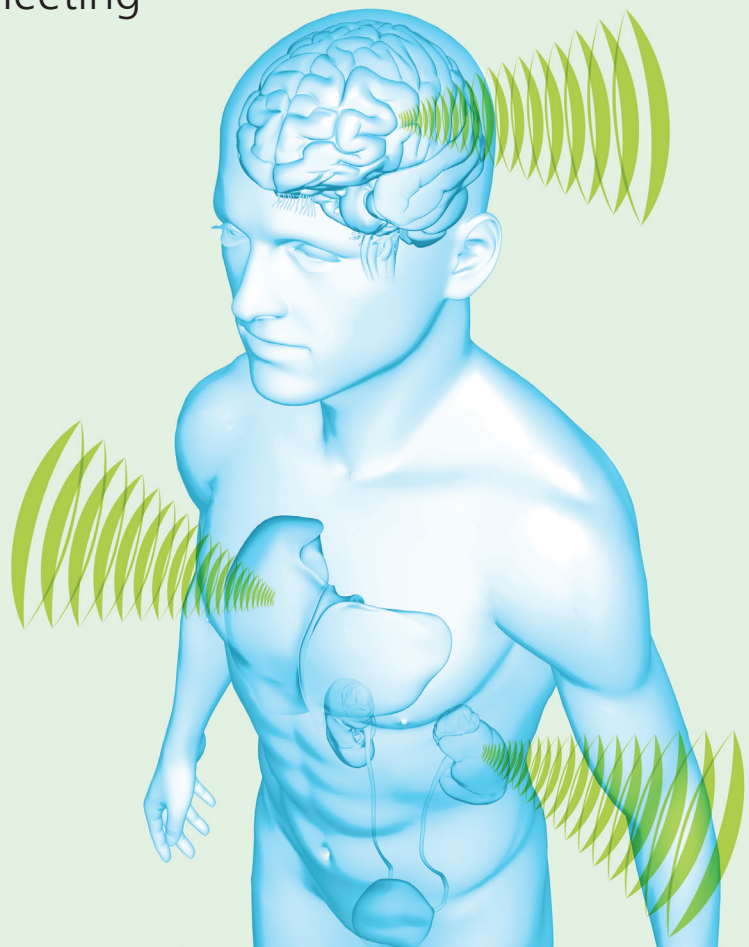
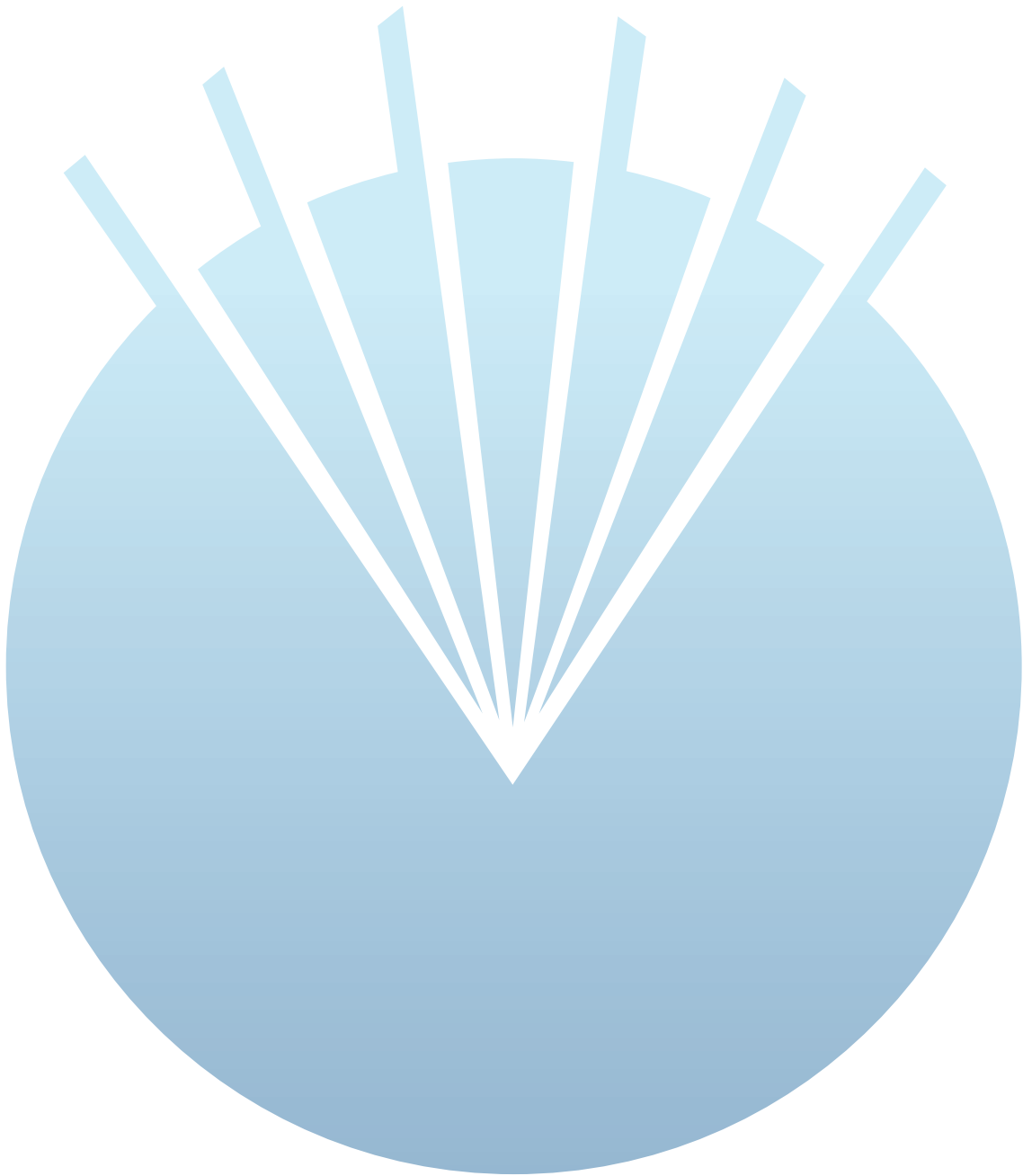


7th International Symposium on **Focused Ultrasound**

November 9–13, 2020

Virtual Meeting





Contents

Monday, November 9, 2020

- 4 **Welcome**
- 5 **Honorary President's Address**
- 6 **Keynote Speaker**
Ralph Northam, *Governor of Virginia*
- 7 **Movement Disorders**
 - 7 Oral Presentation Q&A
- 9 **Parkinson's Disease**
 - 9 Panel
- 12 **Neurodegenerative Diseases**
 - 12 Special Lecture
 - 13 Oral Presentation Q&A
 - 16 Panel
- 18 **Epilepsy**
 - 18 Oral Presentation Q&A
 - 19 Panel
- 21 **Psychiatric Disorders**
 - 21 Special Lecture
 - 22 Oral Presentation Q&A
 - 24 Panel
- 27 **Neuromodulation**
 - 27 Oral Presentation Q&A
 - 28 Panel
Focused Ultrasound for Neuromodulation
Considerations for Human Translation Panel

.....

Tuesday, November 10, 2020

- 33 **Brain Tumors**
 - 33 Oral Presentation Q&A
 - 36 Panel
- 39 **Keynote Speaker**
James Allison, MD, *Anderson Cancer Center*
- 41 **Cancer Immunotherapy**
 - 41 Brain Oral Presentation Q&A
 - 43 Breast Oral Presentation Q&A
 - 46 Other Oral Presentation Q&A
 - 49 Panel
- 52 **Fireside Chat**
Cancer Therapy: *Beyond Ionizing Radiation*
- 53 **Special Lecture**
Liquid Biopsy
- 54 **Special Session**
International Society for Therapeutic Ultrasound (ITSU)

.....

Wednesday, November 11, 2020

- 56 **Keynote Speaker**
Michael Milken, *Milken Institute*
- 56 **Breast Cancer**
56 Panel
- 58 **Prostate**
58 Special Lecture
59 Oral Presentation Q&A
61 Panel
- 65 **2020 Awards Ceremony**
65 Visionary Award
66 Ferenc Jolesz Memorial Award
67 Andrew J. Lockhart Memorial Prize
68 Young Investigator Award Recipients
- 72 **Pancreatic Cancer**
72 Oral Presentation Q&A
74 Panel
- 76 **Liver**
76 Oral Presentation Q&A
- 77 **Miscellaneous Tumors**
77 Oral Presentation Q&A

.....

Thursday, November 12, 2020

- 79 **Keynote Speaker**
Clifton Leaf, *FORTUNE*
- 80 **Blood–Brain Barrier Opening**
80 Technical Oral Presentation Q&A
83 Other Oral Presentation Q&A
- 87 **Drug Delivery**
87 Oral Presentation Q&A
90 Panel
- 93 **Fireside Chat on Gene Therapy**
- 94 **Miscellaneous Indications**
94 Oral Presentation Q&A
- 96 **Musculoskeletal Applications**
96 Oral Presentation Q&A
98 Panel
- 100 **Chronic Pain**
100 Oral Presentation Q&A
- 101 **Women’s Health**
101 Panel

.....

Friday, November 13, 2020

- 104 **Keynote Speaker**
Omar Ishrak, *Intel*
- 105 **Track A**
 - 105 Investor Ecosystem 101
 - 106 Navigating the Investor Ecosystem
 - 107 Business Models 101
 - 108 Business Model Trends in the MedTech Industry
 - 109 Dancing with a Giant
Tips for Productive Relationships Between Startups and Corporates
 - 110 Exits
Considering IPOs vs Acquisitions vs Mergers
- 112 **FDA Town Hall**
 - 112 How to Engage with the FDA
 - 114 The Power of Advocacy Organizations
 - 118 Regulatory
Medical Devices and Combination Products
 - 120 Medicare Reimbursement Pathways for FUS
 - 121 How Medical Specialty Societies Influence Reimbursement
 - 122 Real-World Examples of FUS Site Success
 - 122 Panel
 - 127 Training Certification and Credentialing
 - 127 Panel
- 131 **Track B**
 - 131 Brain Technical—Imaging
 - 131 Oral Presentation Q&A
 - 132 Panel
 - 135 Brain Technical—Miscellaneous
 - 135 Oral Presentation Q&A
 - 137 Brain Technical—Beyond Ablation
 - 137 Panel
 - 140 Technology Research
 - 140 Oral Presentation Q&A
 - 143 Technology Gaps & Breakthroughs
 - 143 Panel
- 146 **Closing Remarks**

.....

Presentation Take Home Messages

- 147 **Symposium 2020 Scientific Program**

**Monday,
November 9, 2020**



Neal F. Kassell, MD

Founder and Chairman,
Focused Ultrasound Foundation

Welcome

Neal F. Kassell, MD, founder and chairman of the Focused Ultrasound Foundation, welcomed the more than 1,700 participants from 57 countries to the symposium.

This year, the meeting called for a robust and multifaceted program that reflected the astronomic growth in the field. In the past, content was presented over the course of three-and-a-half days; it has now been stretched to five days to accommodate all of the expanding topics plus sessions organized by the International Society for Therapeutic Ultrasound (ISTU) and the National Institute of Mental Health (NIMH). A full day devoted to the commercialization aspects of the technology further demonstrates this tremendous growth.

The challenges of an entirely virtual symposium are many, and technology cannot replace the personal interaction that leads to partnerships, collaboration, friendships, and the sense of community that makes this field so special and productive. Therefore, the next symposium in 2022 will be a hybrid format to incorporate this new and modern approach that allows such a large number of individuals to participate and contribute.

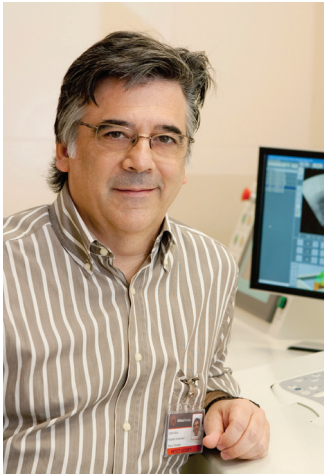
We all share a common vision to improve the lives of millions of people around the world with a wide variety of medical disorders using a revolutionary therapy called focused ultrasound. Along the way, we are creating a multibillion-dollar industry. The dialog has clearly shifted from *IF* focused ultrasound will have an important role in the therapeutic armamentarium to *WHEN*. The revolution is happening. The COVID-19 pandemic has created a worldwide crisis. The foundation's mantra has been, "In these difficult times, we thrive, not just survive." The Chinese character for crisis has two components: risk and opportunity. It is important to focus on opportunities.

.....

Honorary President's Address

Joan Vidal-Jové, MD, PhD

Institut Khuab for Interventional Oncology



Joan Vidal-Jové, MD, PhD

Dr. Vidal-Jové presented “Strategies of Intrusion, Anonymity, and Resistance: The Paradigm of Pancreas Cancer.” Because standard treatments have been largely unsuccessful in the pancreas, focused ultrasound may be a modality that can make a difference.

Pancreatic cancer is the most challenging gastrointestinal malignancy because it is diagnosed late, it is in a difficult anatomic location, it is encapsulated by a strong stroma, and it has a low mutational burden that makes it resistant to immunotherapies. Using chemotherapy presents a multitude of clinical challenges, such as recurrence after treatment, unbearable toxicities, low uptake, and others. The current standard of care is a combination treatment with radiotherapy, chemotherapy, immunotherapy, and stromal therapy. The tumor cycle for pancreatic cancer shows how it evades the immune system.

Focused ultrasound may be able to address several areas of the pancreatic cancer tumor cycle, including disrupting the tumor microenvironment, weakening its fibrotic tissue, unveiling it to the immune system, delivering treatments, and creating immunity. Vidal-Jové asked, “Is ablation the key to these solutions, or just tumor disruption?” He presented the following studies as evidence of the work that is currently under way using focused ultrasound’s capabilities to generate heat, deposit energy, and produce radiation forces:

- Focused ultrasound enhances the delivery of chemotherapy. See Dimcevski et al., *J Control Release*, 2016;243:172–181.
- Immunotherapy can be induced with focused ultrasound hyperthermia. See Toraya-Brown and Fiering, *Int J Hyperthermia*, 2014;30(8):531–539, and Oei et al., *Int J Hyperthermia*, 2017;33(4):419–427.
- Focused ultrasound ablation can reduce pain and ablate select cancer cells. See Marinova et al., *Rofa*, 2019;191(3):216–227, Mittelstein et al., *Appl Phys Lett*, 2020;116:1, and Schibber et al., *Proc R Soc A*, 2020;476:20190692.
- Focused ultrasound has the potential to impact many areas of treatment. See Maloney et al., *Int Rev Immunol*, 2017;36(6):338–351.

There is a long list of focused ultrasound parameters that have been used to create immune-adjunct effects in the preclinical research setting. For the past 67 years, researchers across many disciplines have been seeking the holy grail of cancer immunotherapy: the abscopal effect. More papers on this topic have been published in recent years, including Vidal-Jové’s case report of a 67-year-old man with colorectal liver metastases who showed an abscopal effect after focused ultrasound ablation of the liver. In this case, a focal treatment produced a systemic effect in the same organ.

In the realm of focused ultrasound, histotripsy is showing promise as a precise, fast, and selective modality that is producing measurable immune effects. Vidal-Jové and his group recently completed a successful clinical trial in patients with liver cancer using the HistoSonics device.

• • • • •

Keynote Speaker

Ralph Northam

Governor of Virginia



Ralph Northam, MD

Governor Northam expressed his appreciation to the Focused Ultrasound Foundation for creating robust focused ultrasound activities across the state. Exciting research and development activities are underway at the University of Virginia in Charlottesville and at Virginia Polytechnic Institute and State University in Blacksburg. Patients at the University of Virginia Hospital and the Johnston-Willis and HCA Hospitals in Richmond are being treated with focused ultrasound. The foundation's first Focused Ultrasound Center of Excellence was established 10 years ago at the University of Virginia through a public-private partnership. The Commonwealth of Virginia has been and continues to be a strong supporter of focused ultrasound development, investing \$19 million in the technology over the years. This investment has attracted more than \$40 million in additional private and public funding and established the state as an important international center of biomedical innovation. The Focused Ultrasound Foundation's global reach and impact demonstrate that investing in bioscience and medical technology boosts the economy, fuels job creation, and helps patients worldwide by decreasing the costs of care and improving patient outcomes. The creation of this new industry is literally transforming medicine and the way that many diseases are treated, and it's happening right here in Virginia—the number one state in which to do business, thanks to entities like the Focused Ultrasound Foundation. Governor Northam thanked attendees for participating in this important event and for all that they do individually and collectively to advance this technology.

.....

Movement Disorders

Oral Presentation Q&A

Presentations reported results of clinical research on magnetic resonance guided focused ultrasound (MRgFUS) and thalamotomy (FUS-T) to treat essential tremor (ET).

MODERATORS

Paul Fishman and **Dheeraj Gandhi**, University of Maryland School of Medicine

SPEAKERS

Kyung Won Chang, Yonsei University College of Medicine, Severance Hospital

Feasibility and efficacy of magnetic resonance-guided focused ultrasound surgery (MRgFUS) with autofocusing (AF) echo imaging

Ayesha Jameel, Imperial College, London

The world's first bilateral, staged MRgFUS treatment of medically refractory ET targeting both the ventralis intermedius nucleus and the zona incerta with 12 months follow-up results

Targeting the zona incerta in addition to the ventralis intermedius nucleus with MRgFUS to treat medically refractory essential tremor: Outcomes at 2 years

Raul Martinez Fernandez, CINAC, Hospital Univ. HM Puerta del Sur, Móstoles, Universidad CEU-San Pablo, Spain

Safety and efficacy of focused ultrasound staged bilateral thalamotomy for essential tremor

Francesco Sammartino, Ohio State University Wexner Medical Center

Connectivity changes in tremor network associated with unilateral focused ultrasound thalamotomy
Optimal parameters for focused ultrasound thermal neuromodulation

1 Question to Dr. Martinez Fernandez

What is the source of the differences and adverse effects in previous studies of FUS-T?

Side effects are related to bilateral lesions, especially impaired speech. These lesions were made with radiofrequency, necessitating opening the skull, which gives less control of the lesion. The problem is more invasive lesions. Side effects are related to the invasiveness of the whole procedure rather than to the lesion itself. Gait imbalance is transient and vanishes after 1 to 3 months. It's the difference between a surgical approach rather than a focused lesion.

2 Question to Dr. Jameelz

Your study used a combination of ZI and VIM. There is greater precision with a nonlesion process, so you can get below the coordinates of VIM.

This was the first time our team used the procedure. Some side effects including gait imbalance and speech impairment are due to location. Stereotactic coordinates have been used, but we will start with autofocusing by the end of the year. We have not tried the method on Parkinson's disease patients.

3 Question to everyone

Does anyone use ultrasound imaging rather than MRI?

Dr. Martinez Fernandez uses it for general imaging, but not targeting because the accuracy is not good enough for targeting, although it is promising.

Dr. Jameel's group is working toward that, but they haven't done it yet.

4 Question to Dr. Chang

For this project how did you use computed tomography (CT) data; were they corrected or uncorrected?

We evaluated CT images for every patient and compared that with autofocusing technique. Autofocusing was the better method.

5 Question to Dr. Sammartino

For connectivity-based analysis, where was stimulation coming from? How are the techniques you used different from others?

We analyzed lesions in the cortical areas associated with lesions, but we don't have a large enough [number of] beta sites to test this hypothesis. All the lesions in our center are projected on the human connector.

.

Parkinson's Disease

Panel

MODERATOR

Paul Fishman | University of Maryland School of Medicine

PANELISTS

Howard Eisenberg | University of Maryland School of Medicine

MR-guided FUS update—Parkinson's disease multicenter trials

Jin Woo Chang | Yonsei University College of Medicine

Factors affecting thermal lesioning with MRgFUS for movement disorders

Elisa Konofagou | Columbia University

FUS-mediated brain protein, antibody and gene delivery in early-stage Parkinson's disease

Michael Kaplitt | Cornell University

Nir Lipsman | Sunnybrook Research Institute

José Obeso | CINAC, Hospital Univ. HM Puerta del Sur, Móstoles, Univ. CEU-San Pablo

Two types of ultrasound treatments for applications in Parkinson's disease

Howard Eisenberg from University of Maryland School of Medicine, updated participants on multicenter trials of magnetic resonance-guided FUS (MRgFUS) to treat Parkinson's disease (PD): a pilot study, a pivotal study, and a clinical study. Outcome criteria in all three studies were management of medically refractory dyskinesia. Dyskinesias and motor fluctuations were observed. The clinical study is nearing completion, but COVID stopped collection of outcome measures. Results in all three studies were similar. Next steps are bilateral treatment for bilateral essential tremor and to target alternative sites.

Jin Woo Chang from Yonsei University College of Medicine reported factors affecting 2- and 4-year outcomes of thermal lesioning with MRgFUS for movement disorders in 250 patients. Factors related include skull density ratio and skull volume, and incidence angle for making the lesion. In their solution, the skull was virtually reconstructed using an auto-focusing echo imaging technique. Technical factors included repetition numbers resulting in high temperatures. Thermal ablation is used to treat PD, essential tremor, pain, obsessive-compulsive disorder, and other psychiatric disorders. Nonthermal effects include the blood-brain barrier (BBB) opening, immune modulation, targeted drug delivery, and neuromodulation. Mechanical effects include stroke.

Elisa Konofagou from Columbia University presented FUS-mediated brain protein, antibody, and gene delivery in early-stage PD. BBB is the main obstacle separating vasculature from surrounding tissue of the brain. It is regulated by inductive properties of neighboring cells of the neurovascular unit. FUS-mediated neurotrophic protein and gene delivery induced neurorestoration in the dopaminergic neuron in a mouse model of early stage PD. Single- and multiple-session protein delivery increased dendritic density while

only the multiple-session increased terminal density (up to 50%). Gene delivery required only a single session and demonstrated restored functionality of the entire dopaminergic neuron with behavioral motor testing 3 months after adeno-associated virus (AAV) delivery. Antibody delivery was increased by 3 times and α -synuclein density was reduced by 3 times in the FUS-treated α -synuclein model.

José Obeso from CINAC, Hospital Univ. HM Puerta del Sur, Móstoles, Universidad CEU-San Pablo, discussed two types of ultrasound treatments for applications in PD. High-frequency FUS results in high skull/brain penetration, but skull temperatures can reach 60°C. FUS ablation can be used if applied early. Alternatively, low-frequency FUS can be used with the Exablate transducer and microbubbles to open the BBB. Significant factors included altering the bubble-power balance and targeting large volumes.

1 Question to Dr. Eisenberg

What is the way forward to achieving FUS in patients affected on both sides?

Current techniques may be better tolerated than were used in the 1990s, but the published data are still well below what one would want. This has to be done very carefully with appropriately selected patients. We need to know whether humans can perform without the pallidothalamic output to the rest of the brain. A study in Switzerland of the pallidothalamic (H1) tractotomy on 15 of 40 patients shows that treated patients are doing well. Many idiosyncrasies occurred on the first side; 2 years later the thalamotomy was done on the second side. Fascinating results could be influencing some of the bilateral things happening. Thalamotomy may be better tolerated than pallidothalamic. This might be done every 6 months.

2 Question to Dr. Chang

Why is the blood-brain barrier opening more pronounced in nonhumans?

This is a technical outcome—dosing and control or dosing and concentration of microbubbles. It is a matter of adapting the methodology. We may be seeing inclusive frequency of large vascular spaces. They are not in the cortex, but in PD patients we encounter difficulties. It may be a feature of advanced PD or a nonhuman primate feature.

3 Question to Dr. Konofagou

In your AAV studies, have you noticed differences in the long-term transduction of the vector dependent on the capsid or vector characteristics? What is the duration of action and optimal vector for long-term treatment?

The strain of AAV depends on what you want to achieve. Humans have been exposed to these viruses in a way that animals have not. Strains may matter in terms of their properties and to what the human may have been exposed. All strains worked (although 89 is most efficient with mice). A larger titer was delivered and higher number of neurons used. Direct injection also improves results. In addition, the promoter influences expression in other organs, which is an important issue with the Food and Drug Administration (FDA). One study saw 95% targeting in the neurons. Different centers have to find what is practical (including considering local regulations) and scientifically sound. This is an

iterative process guided by sound data. This procedure combines a new device and a novel therapy. Key is the data package you provide to regulators. The more you deviate from standard practice, the harder it is to get approval, but not impossible.

4 Question to Dr. Obeso

Can you comment on whether deep brain stimulation or the subthalamic nucleus stimulation approach is preferable in PD patients?

Even though the gene setup can be useful, this will be possible for 5 to 10 years. There are many difficulties with using pallidotomy for PD. Even though the patient may have a high score, sometimes it was not possible to make a lesion. Patients with symptoms on one side may be selected, but bilateral lesions could be problematic. It is more a decision of which is best for each patient. Evidence for DBS is poor, and the evidence is in two different leagues. He and colleagues have a paper coming out on this.

• • • • •

Neurodegenerative Diseases

Special Lecture

Merit Cudkowicz, MD

Massachusetts General Hospital

Therapeutic advances in neurodegenerative disorders: ALS as an example



Merit Cudkowicz, MD

Dr. Cudkowicz described ALS and its current standard of care, which consists of four FDA-approved pharmaceutical medications. She noted, however, that recent genomic research had produced multiple therapeutic targets, and more than 150 drug companies were currently developing products to treat ALS. Importantly, the biology that leads to ALS can also be found in many other neurodegenerative diseases, such as Alzheimer's and Parkinson's.

The Northeast Amyotrophic Lateral Sclerosis (NEALS) Consortium is a group of 137 centers that joined together to conduct clinical trials and develop open-source outcome measures and data resources to push the field forward. Similar consortia have formed for Huntington's, Parkinson's, Alzheimer's, and other neurodegenerative disorders. NEALS's innovative platform approaches and cohort enrichment have increased the likelihood of success in neurodegenerative clinical trials.

Cohort enrichment can be done using a homogenous group of study participants or by choosing participants who are biologically more likely to respond to treatment. A combination-therapy clinical trial on a homogenous cohort was recently conducted at Massachusetts General Hospital. In this group, the novel agent, AMX0035 (a proprietary, oral combination of two drugs already in use, sodium phenylbutyrate and tauroursodeoxycholic acid), significantly slowed the rate of decline and loss of function in patients with ALS. Furthermore, the study showed that early intervention reduced the risk of death in the group of patients originally randomized to receive AMX0035 by 44 percent and extended the median survival from 18.5 to 25.0 months with a follow-up period of up to 36 months. Gene therapy approaches are those that are suited for biologically based patient cohorts. An example of this type of study is the Biogen phase 1–2 antisense oligonucleotide “Toferson” for patients with SOD1 ALS. This successful trial hit its safety targets, improved outcomes, and has now moved into phase 3, and its neurofilament level decreases have implications for other neurodegenerative diseases.

Innovative, patient-centric platform trials, such as Massachusetts General Hospital's HEALEY ALS Platform Trial, can provide more treatment options with fewer placebos. This clinical trial platform cut costs and time by using a shared infrastructure, common protocol, and randomization to test multiple drugs while enrolling an increased number of participants in the active regimen groups (e.g., 75% active drug, 25% placebo). Patients, investigators, research sites, industry, and the FDA are all enthusiastic about this approach. The plan is to add new therapeutics to the platform each year.

In summary, the platform trial approach can greatly accelerate the path to new treatment options. It has strong support across the drug development ecosystem, and it will continue on as a perpetual trial until cures are found.

• • • • •

Neurodegenerative Diseases

Oral Presentation Q&A

The oral presentations highlighted the use of FUS in the potential treatment of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD).

MODERATORS

Sandra Black | Sunnybrook Research Institute

SPEAKERS

Jin Woo Chang | Yonsei University College of Medicine

The preliminary results of a single-center, open, prospective, single-arm, feasibility assessment of initial efficacy and safety of MRgFUS for blood brain barrier disruption in patients with Alzheimer's disease

Jürgen Götz | The University of Queensland

Therapeutic ultrasound as a treatment strategy for improving cognition in physiological and pathological aging

Maria Eleni Karakatsani | Columbia University

Focused ultrasound-induced blood-brain barrier opening mitigates pathological progression, improves spatial memory and initiates cholesterol changes in the 3xTg-Alzheimer's mouse model

Vibhor Krishna | Ohio State University Wexner Medical Center

Safety and initial efficacy of hippocampal blood-brain barrier opening for plaque clearance in Alzheimer's disease

Gerhard Leinenga | The University of Queensland

Aducanumab delivery by focused ultrasound in APP23 mice

Ying Meng | Sunnybrook Health Sciences Centre

Blood-brain barrier opening of multiple and dispersed brain regions using MR-guided focused ultrasound in Alzheimer's disease

Kristiana Xhima | Sunnybrook Research Institute

Delivery of a selective TrkA agonist to the brain using transcranial focused ultrasound enhances cholinergic function and rescues cognition in a mouse model of Alzheimer's disease

1 Question to Dr. Chang

Why did you choose the frontal lobes when using FUS to open the blood-brain barrier (BBB)? Did you use microbubbles or just FUS? What was the percent reduction of positron emission tomography (PET) in those areas?

The frontal lobe is an important structure in the brain and relatively safer to work with than other lobes. The same area was used for each patient. The clinical trial of six patients is not finished, but some promising results have been seen in some patients. Regulations from the Korean government have placed limitations on the use of microbubbles. As far as PET reduction, the data have not yet been analyzed; results are expected by the end of the year.

2 Question to Dr. Götz

Were there particular areas of the brain that seemed to show more benefit than others?

The research focused on the hippocampus only and improvements were found in neuronal signaling. Changes seen biochemically were indicative of those found electrophysiologically.

3 Question to Dr. Götz

Were there particular areas of the brain that seemed to show more benefit than others?

The research focused on the hippocampus only and improvements were found in neuronal signaling. Changes seen biochemically were indicative of those found electrophysiologically.

4 Question to Dr. Leinenga

Why do you think the combination of techniques with microbubbles and the antibody aducanumab is working in your mouse model? And why did it work more effectively in the cortex vs. the hippocampus?

Previous studies had shown that ultrasound without an antibody was able to reduce plaques and that aducanumab was effective at removing plaques when given as an intravenous injection. The results of the study comparing ultrasound, aducanumab, and the combination showed that behavior and plaque removal in the cortex were better with the addition of the antibody than with BBB opening alone. All of the treatments reduced plaques in the hippocampus but had differential effects on behavior. The differences in the results in the cortex and hippocampus could be related to how the ultrasound was delivered, the amount of BBB opening in the different regions, and the consistency of the opening in the different regions.

5 Question to Dr. Leinenga

Did you see amyloid-related imaging abnormalities in the rodents?

Yes, bleeding from amyloid pathology was seen in older mice, but this did not seem to be enhanced by antibody treatment or ultrasound. There were no marked differences between the groups.

6 Question to Dr. Karakatsani

Why did you see effects on just the wild-type mice and not the pathological model? What is the implication of looking at cholesterol?

The wild-type mice were used as a control to determine whether the FUS-induced BBB opening alone would cause any behavioral changes, and it did. This is being explored further to see whether the effect on the transgenic animals is solely dependent on the reduction in pathology or on an improvement in memory associated with FUS alone. Cholesterol changes have been implicated in amyloid plaque reduction in the brain and, in this study, LDL increased after FUS. This finding will be discussed in an upcoming paper.

7 Question to Dr. Karakatsani

Can you explain why the effects of tau on neuronal length decreased with treatment?

This was a follow-up to a previous study using an animal model that only expresses phosphorylated tau. In this model, the axonal projections were less affected by tau

after repeated FUS. That is also the case when amyloid is present. Despite mild amyloid reduction, tau decreased significantly.

8 Question to Dr. Xhima

What is D3? Are there analogs in humans?

The BBB opening was induced with FUS and microbubbles, coupled with delivery of a TrkA agonist called D3. TrkA is a receptor for nerve growth factor, which is implicated in regenerative processes related to the cholinergic system, a key neurotransmitter system that degenerates in AD. D3 also binds to human TrkA and is already being used clinically for other applications, such as retinal degeneration. The next step will be to identify patients with an underlying TrkA deficit who could potentially benefit from this treatment.

9 Question to Dr. Krishna

Were all of the patients in your study positive on PET? And did the cognitive and behavioral adverse events resolve?

The study looked at opening the BBB with an infusion of microbubbles in patients with AD, initially focusing on the hippocampus. As the study expanded to other regions of the brain, all patients were PET-positive for amyloid. Changes in amyloid varied after three treatments. Most of the cognitive and behavioral effects resolved. The working memory of one patient is being followed.

10 Question to Dr. Meng

Your study now has nine subjects with multiple BBB openings. Have there been any adverse events?

There were no serious adverse events. Some patients had a transient period of increased confusion that may be related to some anesthetic effects of the procedures. Overall, the procedure was well-tolerated.

.

Neurodegenerative Diseases

Panel

MODERATOR

José Obeso | CINAC, Hospital Univ. HM Puerta del Sur, Móstoles, Universidad CEU-San Pablo

PANELISTS

Ying Meng | Sunnybrook Health Sciences Centre

Early clinical experience with BBBO and AD and lessons learned

Jürgen Götz | The University of Queensland

Opportunities and challenges of treating Alzheimer's Disease with therapeutic ultrasound

Nick Todd | Brigham and Women's Hospital

Enhancing gene therapy delivery across the blood brain barrier for treatment of neurodegenerative diseases

Ying Meng from Sunnybrook Health Sciences Centre is using MR-guided FUS in patients with AD to open the BBB and deliver therapies noninvasively to large regions in the brain. Her goal is to understand how to deliver FUS to patients safely and with adequate feedback, and to open the BBB to deliver therapeutics without causing hemorrhage. She is also looking at how BBB openings in widespread areas of the brain affect biological markers.

Jürgen Götz from the University of Queensland is exploring the treatment of AD with FUS together with intravenously injected microbubbles in a model using older mice. He noted that clinical trials in AD research have been dominated by a focus on amyloid pathology, but an important question is whether the driver of the disease is related to amyloid, tau, or something else. Amyloid-beta, which is extracellular, is an easier therapeutic target than tau for therapeutic ultrasound.

Nick Todd from Brigham and Women's Hospital is using FUS to deliver gene therapies to the brain through opening the BBB. He is looking at some of the rarer single-gene disorders such as HD and lysosomal storage disorders that have neurological manifestations and clear targets. He is currently working with delivery efficacy in mice. The next step will be showing safety and delivery efficacy in nonhuman primates before moving to clinical trials.

1 Question to Dr. Todd

How do you know that delivery of therapeutic agents to the striatum and/or cortex in Huntington's disease will be effective?

The striatum is targeted because that is where the disease manifests initially. HD is a whole brain disease and many later deficits come from cortical degeneration. To fully treat the disease, the cortex will need to be included as well. The challenge is in not only delivering FUS to one region but targeting multiple brain regions as well.

2 Question to all

How do we deal with differences in in the uptake of therapeutic agents by different brain areas or cell types? Tau clearance and the uptake of anti-tau antibodies are often confined to certain brain areas. Why?

Dr. Todd: This may be a question of delivery, i.e., of not opening the BBB as much in these areas, or of uptake and retention.

Dr. Götz: A therapeutically delivered agent needs to be retained and engage with the target. Even with consistent BBB opening, there are differences in uptake of the therapeutic antibody.

3 Question to Dr. Götz

Many studies have tried to reduce amyloid in the brains of patients with AD and have failed. Is this a concern at this early stage of studying BBB opening and therapeutics?

The argument has always been that treatment is too little too late. In the clinical setting, the issue may be in not delivering enough antibody. This is an area where FUS can help. It may also allow for the possibility of combining two antibodies without reaching toxic levels for each. FUS can also be used on its own (without a therapeutic agent) by using microbubbles. The beauty of FUS is that different mechanisms can be activated.

4 Question to Dr. Meng

Do you see the applications of FUS as just local or a succession of events?

In HD, for example, it would be wonderful to modify the sequence of events earlier.

This is certainly possible. The effects of FUS are not just local. Changes have been seen in fluid attenuated inversion recovery (FLAIR) signals, for example, indicating changes in pathways. Changes in biomarkers and changes at a more systemic level have also occurred. So FUS probably has more widespread effects.

5 Question to Dr. Todd

What are your expectations for administering adeno-associated viruses (AAVs) through the BBB opening vs. direct injection?

The advantage of using FUS compared with direct injection (a one-time procedure) is the ability to target one brain region. FUS can be used repeatedly because it is more cost-efficient, less invasive, safer, and allows for getting an appropriate concentration in multiple brain regions. The main challenge with AAVs is the host immune response; delivery may not be as successful in subsequent administrations. For gene therapies, it will be challenging to get whole-brain coverage, which is needed for many neurodegenerative diseases.

6 Question to Dr. Meng

The procedure for using MR-guided FUS in patients requires a frame. Do you see the possibility of going frameless and doing this repeatedly?

Many technical modifications are needed. The frame and hair-shaving need to improve for patients to tolerate the procedure and agree to monthly treatments.

.

Epilepsy

Oral Presentation Q&A

Presentations addressed the feasibility of treating human epilepsy using magnetic resonance-guidance technology, thalamic ablation, and neuromodulation with FUS.

MODERATOR

Nathan Fountain | University of Virginia

SPEAKERS

Sijia Guo | North Carolina State University

Investigating the feasibility of MRgFUS for minimally invasive heating of mesial temporal lobe structures

Vibhor Krishna | Ohio State University Wexner Medical Center

Focused ultrasound ablation of the anterior thalamus for epilepsy

Hsiang-Yu Yu | Taipei Veterans General Hospital

Safety and feasibility of neuromodulation for drug-resistant epilepsy by low intensity focused ultrasound, an intracranial EEG study

1 Question to all

What final words can you offer?

Dr. Krishna: Seizure frequency dropped by 20%; then 40% at 3 months. Ultimately 50–60% of patients experienced fewer seizures from 4 months to 3 years. MRgFUS is a potential therapy for treatment-resistant epilepsy. The goal is to test for seizure reduction, not seizure freedom.

Dr. Yu: LIFUS is safe and feasible in neuromodulation of a targeted region. The response was dose-dependent in one instance.

.

Epilepsy

Panel

MODERATOR

Nathan Fountain, University of Virginia

PANELISTS

Michael Sperling | Thomas Jefferson University

Ablation of small targets for epilepsy

John Rolston | University of Utah

The case for noninvasive epilepsy surgery

Vibhor Krishna | Ohio State University Wexner Medical Center

A pilot open-label clinical trial evaluating focused ultrasound thalamotomy for the prevention of secondary generalization in focal onset epilepsy

Robert Fisher | Stanford University

Current neuromodulation for epilepsy

Hsiang-Yu Yu | Taipei Veterans General Hospital

NaviFUS emerging clinical study

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

Potential of microbubble-enhanced FUS for epilepsy

Michael Sperling from Thomas Jefferson University presented ablation of small targets for epilepsy, beginning with cross-sections of the cadaveric brain. His uncontrolled data are encouraging. They now know that ablation can effectively treat small lesions. Various techniques are available. FUS merits further investigation. However, laser thermal ablation is expensive and not covered by insurance.

John Rolston from the University of Utah presented the case for noninvasive epilepsy surgery. He reported on three randomized studies that show that surgery is better than drug treatment: 60%–70% of patients were seizure-free at 1 year. However, it currently takes an average of 20 years for a patient to get a referral for surgery. We need education and outreach to increase use of this less invasive and more effective technique.

Robert Fisher from Stanford University discussed neuromodulation to treat epilepsy. Current therapy consists of medication, diet, biofeedback, and surgery. Neuromodulation avoids tissue destruction, neurological function is preserved, and it can be done in stages. If it fails, the patient can resort to surgery. It is possible with bilateral seizure foci.

Nathan McDannold from Brigham and Women's Hospital presented a study of the potential of microbubble (MB)-enhanced FUS for epilepsy. A strong microbubble response concentrates ultrasound effects on the vasculature. MB-enabled autofocusing was used to improve transcranial focusing. Nonthermal ablation via MB-enhanced FUS destroys blood vessels with MB-enhanced sonication. Acoustic exposure is reduced by more than an order of magnitude.

1 Question to all

What is the way forward?

Dr. Fisher: For autofocusing, the challenge is the huge variability in patients, but heat is not an issue. Stereotaxic radiosurgery was tried on two patients who both improved.

Dr. Sperling: Good targets could include small hamartomas, like those that occur in the hypothalamus, and also heterotopias because of their size. Periventricular nodules could also be considered. For repeated ablation, think about targeting small lesions. It involves intracranial electrodes, but surgery made all three patients seizure-free. The more anterior medial ablations seem to be better. You do not need to take the whole hippocampus. Considering it to be a hippocampal disease would be too restrictive. For spike suppression, some investigators have tried encasing a drug in a polymer. The polymer goes everywhere but affects nothing; ultrasound “cracks” the polymer.

Dr. Krishna: With FUS thalamotomy, 6–8 mm is the largest area that can be reached so far, and it would take five or six of these lesions to cover the thalamus. Time would become an issue, and that does not take into consideration skull heating. We need effort to find the best targets. The individual ability to hit tissues in repeated treatments may differ. Ability to heat tissue may be much better. There also may be a previous-exposure effect.

Dr. Fountain: Most patients have lesions in the cortex rather than the temporal region.

Dr. McDannold: We also need to tackle the skull effects. With ablation we can measure what we’re doing. We need improvements in technology, and FUS will become faster and more focused.

Dr. Yu: The size of the transducer is an issue. Size and energy of the focused ultrasound beam are not so big and not so strong.

Dr. Rolston: More experimental therapies will lead to using them diagnostically as well as therapeutically.

• • • • •

Psychiatric Disorders

Special Lecture

Renana Eitan, MD

Brigham and Women's Hospital

Focused Ultrasound for Psychiatric Disorders



Renana Eitan, MD

In this special lecture, Dr. Eitan said that focused ultrasound is needed to address mental disorders because they are common, increasing in incidence, highly debilitating, and a major cause of suffering around the world. New treatment options that are effective, safe, and available to a large population are needed because up to one-third of psychiatric patients do not reach remission despite the availability of optimal treatments.

Brain circuits in mental processing are an important key to treating mental disorders because they connect the cortical and subcortical regions of the brain. Specific circuits are related to salience, negative affect, positive affect, attention, and cognitive control. Focal targets for neuromodulation might be based on the way that information converges for processing at the basal ganglia as it is passed from the cortex via the cortical-striatal pathways; therefore, each of these areas could be a target for neuromodulation. Any psychiatry target should be specific to limbic or cognitive networks.

There are several methods for using neuromodulation in psychiatry. Cortical neuromodulation is applied either electrically or magnetically, whereas subcortical neuromodulation is applied electrically using deep brain stimulation (DBS) or invasively using mechanical or thermal ablation. Focused ultrasound is the only noninvasive method of transcranial thermal ablation for the subcortical region.

Anterior capsule ablation has been used as a type of neuromodulation for obsessive-compulsive disorder (OCD) for many years. The lesions and clinical outcomes when using gamma knife, DBS, open capsulotomy, and focused ultrasound have been shown to be similar. Significant clinical effects, as measured with the Yale-Brown Obsessive Compulsive Scale (YBOCS), take 6 to 12 months to develop for each of these technologies. To date, 20 patients with severe, treatment-resistant OCD have undergone focused ultrasound capsulotomy in clinical trials.

Advanced imaging techniques, functional imaging, and electrophysiology tests are needed to identify and confirm the exact targets for neuromodulation, and exact targets are necessary for obtaining clinical effects and avoiding adverse events.

In summary, there are many methods of neuromodulation and ablation that are used in psychiatry. With ablation, a capsulotomy can be achieved with invasive thermal ablation, gamma knife, or focused ultrasound; however, focused ultrasound is the only method that is noninvasive, and it has the highest spatial resolution. Neuromodulation can be performed with DBS, deep transcranial magnetic stimulation (dTMS), transcranial direct current stimulation (tDCS), or focused ultrasound. If it can be proven effective, focused ultrasound would be comparable to DBS in effectiveness and spatial resolution, but a completely noninvasive option.

.....

Psychiatric Disorders

Oral Presentation Q&A

Presentations highlighted findings and lessons learned to date from the use of focused ultrasound (FUS) in the treatment of obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). FUS offers new approaches that could benefit patients with the most intractable forms of these conditions.

MODERATOR

Rees Cosgrove | Brigham and Women's Hospital

SPEAKERS

Benjamin Davidson | Sunnybrook Research Institute

Magnetic resonance-guided focused ultrasound capsulotomy for psychiatric disorders: Clinical results and neuroimaging analysis

Jeong-Ho Seok | Yonsei University College of Medicine

Effect of low-intensity focused ultrasound stimulation in patients with major depressive disorder

Norman M Spivak | University of California, Los Angeles

Transcranial focused ultrasound may disrupt amygdalar function

1 Question to Dr. Davidson

Patients have shown cognitive changes following anterior capsulotomy (AC) performed with radiofrequency or gamma knife. Please share insights on why patients in your study of magnetic-resonance-guided focused ultrasound (MRgFUS) capsulotomy showed no significant cognitive changes.

SI suspect this has to do with lesion placement and volume. The FUS procedure makes fairly small lesions in the most ventral aspect of the anterior limb of the internal capsule (ALIC). Cognitive neuropsychological changes may result from dorsal enlargement of the lesion and disconnection of the fibers that travel to the dorsolateral prefrontal cortex and are involved in executive function circuitry. Additionally, unlike open surgery, FUS does not pass through any fibers to reach the ALIC.

2 Question to Dr. Davidson

Please explain the higher treatment response rate among patients with OCD compared with those with MDD.

The neurocircuitry-based rationale for surgery is stronger for OCD. There is more evidence to support the hypothesis that disconnecting the limbic-corticostriatal circuit should help in OCD, whereas there is less evidence for this in depression. The literature within the past 5 to 10 years suggests a response rate of 30% to 50% in patients with depression. Another possible reason for the lower response rate in depression could be its high heterogeneity compared with OCD.

3 Question to Dr. Davidson

What is the mechanism for improved cognition following treatment?

Dr. Davidson said that he did not believe that cognitive improvement is a practice effect (in which results “improve” simply because patients take the same test twice). The team had been careful to avoid practice effects by using alternate versions of tests and administering the second test after an interval of about 7 months. He suspected that if a patient’s condition improves as a result of treatment such as medication or cognitive therapy, he or she can then devote more mental resources to cognitive tasks, resulting in an improvement in cognitive scores. Due to small numbers, the research team could not clearly establish whether MRgFUS capsulotomy has a direct effect on the circuits involved in cognitive processes.

4 Question to Dr. Seok

What is your methodology for targeting the dorsolateral prefrontal cortex (DLPFC), and can you estimate the dimensions of the volume of the target that was being stimulated?

The MRI coordinates were used to target the DLPFC within a diameter of 5 mm from the target.

5 Question to Dr. Seok

Did patients experience any physical sensations that would enable them to distinguish whether they were receiving active or sham treatment?

No participants differentiated active from sham stimulation. He added that he administered FUS stimulation to himself at a frequency of 250 kHz on one occasion and did not experience any physical sensation.

6 Question to Dr. Seok

What is your opinion on how low-intensity FUS compares with other neuromodulatory treatment modalities such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS)?

Dr. Seok replied that his impression is that tDCS is the weakest neuromodulation technique. TMS and low-intensity FUS have similar treatment effects. However, TMS can cause headaches or discomfort for the patient, while low-intensity FUS is comfortable for the patient. Low-intensity FUS is a safe and effective technique for noninvasively activating or deactivating the prefrontal cortex without ablation.

7 Question to Dr. Spivak

Why did you select the particular neuropsychological tests that were used in your study to test neurostimulation?

The research team had consulted Michelle Craske, a co-author who is also on the faculty of the University of California, Los Angeles, for assistance in choosing tests that would enable the detection of both objective and subjective changes in amygdalar function.

8 Question to Mr. Spivak

The entorhinal cortex and the amygdala are situated right next to each other and are folded. How were you and your colleagues able to differentially target these two brain regions?

The team targeted the right amygdala and the left entorhinal cortex. They adjusted the transducer and collected repeated MRI localizers until they were confident that they were aiming at the correct target.

9 Question to Mr. Spivak

How did you and your team determine that the MRI scanner was targeted correctly?

We take a line orthogonal to the surface of the transducer and trace it down into the brain to measure the focal depth of the transducer. Also, arterial spin labeling is done as a sort of biomarker for change in depth.

10 Question to all

Please share your thoughts on the possible mechanism of low-intensity FUS and on what might be the best method of investigating this question.

Dr. Spivak: It is primarily a mechanical rather than a thermal effect. A mechanical effect leading to a stretching of the membrane or the channels might also be involved. Drs. Seok and Davidson agreed that it is probably a mechanical effect.

Dr. Davidson: The starting point for investigating this question would be to perform a series of low-intensity stimulations in an animal model to look for neurochemical changes.

.

Psychiatric Disorders

Panel

MODERATOR

Rees Cosgrove | Brigham and Women's Hospital

PANELISTS

Nir Lipsman | Sunnybrook Research Institute

MR-guided focused ultrasound in psychiatric disease: Proof-of-concept and experience in early phase trials

Ben Greenberg | Brown University

Surgical ablation for intractable OCD: The Rhode Island experience

Renana Eitan | Brigham and Women's Hospital

Focused ultrasound for psychiatric disorders

Darin Dougherty | Harvard Medical School

Nir Lipsman from Stonybrook Research Institute reported that MRgFUS AC offers the opportunity to noninvasively perform a variety of standard neuropsychiatric surgical procedures. Dr. Davidson's work has shown the feasibility of generating two bilateral lesions in the ALIC with MRgFUS AC in patients with treatment-resistant depression and OCD. One year post-procedure, cerebral glucose metabolism was significantly reduced in the dorsolateral prefrontal cortex. Four out of 6 patients with OCD and 2 out of 6 patients with depression responded to treatment, demonstrating 35% to 50% reductions in scores on standard OCD and depression symptom scales. No serious adverse events were observed. Some patients developed transient headaches due to wearing the stereotactic frame for the duration of treatment. In most cases the procedure can be performed on an outpatient basis. It may be more difficult to generate a lesion on the second side in bilateral treatment. Skull characteristics (both density and thickness) may portend varying success rates in generating bilateral lesions. Patients must be

kept sedated and comfortable for the duration of treatment. As is the case with other lesioning procedures for psychiatric indications (e.g., anterior cingulotomy, gamma-knife AC), MRgFUS AC does not generate an acute treatment effect. The time to clinical response is on the order of weeks to months. It is critical that patients continue long-term psychiatric follow-up care to put into context any changes that they may or may not be experiencing. Dr. Lipsman and his colleagues are developing phase 3 trials and are evaluating whether a conventional randomized controlled trial (RCT) design is the optimal approach for measuring efficacy outcomes or whether novel designs are needed. In the future the team is interested in using FUS to treat post-traumatic stress disorder and eating disorders, recalcitrant conditions in which anxiety and mood play a strong role.

Ben Greenberg from Brown University reported that he and his colleagues have posited that two main symptoms—harm avoidance and “incompleteness”—drive the obsessions and compulsions that are the hallmark of OCD. This suggests that there may be two underlying types of OCD, which may in turn relate to surgical outcomes. Less than 1% of treatment-seeking individuals with OCD are candidates for surgery. The most relevant surgical pathways seem to be the ventral and dorsomedial prefrontal cortex to subcortical networks. An estimated 55% to 70% of well-selected patients with intractable illness may experience meaningful benefit from surgery. Long-term outcomes following ablation or deep brain stimulation (DBS) seem roughly similar. The Brown OCD Research Group has obtained encouraging initial data for MRI-guided laser ablation, with 70% of subjects responding fully to treatment. In a 2018 study by Kim et al., 55% of patients (6/11) were full responders to high-intensity FUS.

Renana Eitan from Brigham and Women’s Hospital reported that investigators from Harvard and Stanford are planning to collaborate on a two-stage study to evaluate the safety and efficacy of the Insightec MRgFUS capsulotomy for patients with moderate to severe treatment-refractory OCD. In stage 1, 10 patients will be recruited who will serve as their own controls. In stage 2, 56 patients will be recruited to an RCT of MRgFUS capsulotomy versus sham treatment. FUS holds promise as a novel method of neuromodulation. Reversible subthreshold sonications could be used to screen for potential neuromodulation targets in disorders such as anorexia, schizophrenia, substance abuse, and Tourette’s syndrome, in addition to depression and OCD.

1 Question to all

What are the advantages and disadvantages of gamma-knife AC vs MRgFUS AC in patients with moderate to severe treatment-refractory OCD?

Dr. Cosgrove: MRgFUS AC uses the same target in the same patient subgroup as gamma-knife AC, but it is noninvasive, its lesioning effect is immediate, and it presents no risk of radiobiologic adverse effects.

Dr. Lipsman: Difficulty achieving lesional temperatures bilaterally is a current limitation of MRgFUS technology.

2 Question to all

How can targeting be improved for patients who may be candidates for FUS-based procedures for psychiatric indications?

Dr. Dougherty: A 60%-to-70% response rate has been achieved using standard XYZ coordinates across patient populations. His group at Harvard showed that their target was

at the middle of the bell curve, which extended both dorsally and ventrally up to 8 mm. Future clinical trials should examine whether individual targeting instead of standard XYZ coordinates can further increase response rates.

3 Question to all

Are there markers that could be used preoperatively to predict which patients are likely to respond to MRgFUS AC?

Dr. Dougherty: Studies using tractography or functional MRI could be used to identify possible preoperative biomarkers. Alternatively, analysis of electrophysiological data could identify a marker that would indicate that treatment is being directed to the correct target. Studies using prospective fluorodeoxyglucose positron emission tomography (FDG-PET) scanning found that higher activity in the posterior cingulate cortex predicted response to treatment in patients with OCD, while in patients with depression, higher activity in the subgenual prefrontal cortex predicted response.

Dr. Lipsman: Dr. Davidson's initial studies of preoperative functional connectivity suggest that the connection between the ventral striatum and the hippocampus may differentiate patients who are likely to respond from those who are unlikely to do so.

4 Questions to Dr. Lipsman

Does the patient need to be asleep during the procedure? Would it be feasible to validate the placement of the electrode by having the patient perform a neurocognitive task related to their OCD psychophysiology intraoperatively?

Patients are often sedated to avoid discomfort during the procedure. However, even if the patient is sedated, there are techniques that can be used to identify the brain circuits that are being activated.

5 Question to Dr. Eitan

Are low-intensity FUS stimulation and DBS complementary or antagonistic?

Both the mechanism and the patient population for ablation, DBS, and low-intensity FUS stimulation are different. Low-intensity FUS stimulation is actually similar to TMS, which has been studied in patients with mild to moderate OCD or depression but not in those with the most severe disease. These patients have a different profile from those who are treated with DBS or MRgFUS AC.

6 Question to Dr. Lipsman

What are the most appropriate outcomes to evaluate in clinical trials of psychiatric neuromodulation?

In a recently published article, Dr. Lipsman and his colleagues argued for a re-evaluation of clinical trial outcome measures to reduce the emphasis on pre-post scores on instruments such as the Yale-Brown Obsessive-Compulsive Scale and the Hamilton Rating Scale for Depression, and focusing instead on measures of improvement in quality of life and of the extent to which patients are re-integrated into their families and their workplaces.

• • • • •

Neuromodulation

Oral Presentation Q&A

Presentations addressed methods to modulate brain function.

MODERATORS

Elisa Konofagou | Columbia University

Seung-Schick Yoo | Brigham and Women's Hospital

SPEAKERS

David Attali | Physics for Medicine, INSERM, ESPCI Paris, CNRS, PSL Research Univ., Univ. de Paris, GHU ParisI

Sustained, reversible and specific manipulations of oculomotor performance in non-human primates by neuronavigated transcranial ultrasound stimulation with return to baseline

Hyun-Chul Kim | Brigham and Women's Hospital

FUS-mediated functional modulation of cortical and thalamic motor areas in awake sheep

Taylor Kuhn | University of California, Los Angeles

Low intensity focused ultrasound: A possible non-invasive cognitive neural prosthetic

Martin M. Monti | University of California, Los Angeles

Thalamic low intensity focused ultrasound in acute and chronic disorders of consciousness

W. Apoutou N'Djin | INSERM

FUS-induced calcium fluxes in an in-vitro human neural cell model

Pavel Novak | Storz Medical AG

TPS: Shockwave pulses stimulate the brain

Mehmet S. Ozdas | University Children's Hospital, Zurich

Non-invasive receptor-specific millimeter-precision manipulation of brain circuits by ultrasound-mediated aggregation and uncaging of drug carriers: In vivo results

Lennart Verhagen | Radboud University

Modulating deep brain circuits with low-intensity focused ultrasound

1 Question to Dr. Attali

Were the primates randomized?

Yes, primates were randomized between left and right. Two sets of parameters were used a few years ago. The first time was to induce a sustained effect on the monkeys: the effect of a 40-second stimulation lasted about 2 hours. Total duration was the only condition that changed.

2 Question to Dr. Kim

Did the electromyography tones come back immediately and how repeatable were the observations?

Sheep were working on a treadmill. They recovered to baseline in 30 to 50 seconds. This study reported response rate; repeatability will be tested in the future.

3 Question to Dr. Monti

How long can a minimally conscious state improvement last?

We can only speak to our follow-ups, which were done up to 6 months. Beyond that we cannot estimate. Some do maintain improvement, but others revert. However, this was a small sample size. For the patient, it is often the patient's family who recognizes the difference. We typically have the family with us because their presence often triggers better responses. Sometimes they will say they never saw a particular response. That's when we know something has truly changed.

4 Question to Dr. N'Djin

These are more mechanistic options. Did the parameters vary in vitro?

We tried to stimulate brain cells. Petri dishes are a difficult medium in which to measure those effects, but we can model what is going on. The incidence is changing. We know the pressure in the presence of neural cells is a factor. This was a proof-of-concept study. It is easier to cause effects in vitro than in vivo. Even going from cell cultures to brain slices, the amount changes, but the trends are the same.

5 Question to Dr. Novak

What was the frequency, the wave propagation, and depth of penetration?

A zone about 5 cm deep from the skull. To achieve homogeneous distribution of delivery, we moved to another target after 1 microsecond ~20 MHz. The thickness of the skull must be allowed for.

6 Question to Dr. Ozdas

How is the drug aggregate uncaged?

Bubbles aggregate together and form a shell. Once the ultrasound is applied, the drug aggregate is uncaged.

7 Question to Dr. Verhagen

It is easy to interfere with brain function, but can we enhance function?

Being able to super-boost healthy function is the holy grail, and it is incredibly difficult.

.

Neuromodulation

Panel

Focused Ultrasound for Neuromodulation

Considerations for Human Translation Panel

MODERATOR

Lizzy Ankudowich | National Institute of Mental Health

PANELISTS

Holly Lisanby | National Institute of Mental Health

Funding opportunities for focused ultrasound neuromodulation in mental health

Ellen Bubrick | Brigham and Women's Hospital

Low intensity focused ultrasound for epilepsy

Bin He | University of Minnesota

Electrophysiological source imaging guided transcranial focused ultrasound neuromodulation

Jamie Tyler | IST (isensetec.com)

Neuromodulation by focused ultrasound: Innovation & development from a small business perspective

Greg Clement | U.S. Food & Drug Administration, Office of Science and Engineering Laboratories

Ultrasound neuromodulation: Regulatory research and tools

Pamela Scott | U.S. Food & Drug Administration, Neurostimulation Devices, Psychiatry Branch

Regulatory pathways for investigational devices

David McMullen | National Institute of Mental Health

Seung-Schik Yoo | Brigham and Women's Hospital

Holly Lisanby from the National Institute of Mental Health spoke about research gaps starting with the tool itself and how to use it. We need to be able to probe deep targets and circuits selectively and noninvasively. Begin with proof of concept (when you engage the target you see a change in symptoms). Then define, model, and measure all aspects of delivered dose; evaluation of target engagement should use brain measures; identify what each is expected to do; select equipment to measure target engagement; include sham/control subjects; and use deep-penetrating devices. Funding opportunities at NIH include the Brain Initiative, R61/R33 mechanisms, U01 for cooperative agreements, and funding opportunity announcements (FOAs) to support method development and biomarkers. However, FDA approval doesn't mean the patient's insurance will pay for the procedure.

Ellen Bubrick from Brigham and Women's Hospital discussed LIFUS to treat epilepsy. If surgery is not possible, neuromodulation will be considered. This usually involves vagal nerve stimulation and deep brain stimulation. Responsive neurostimulation occurs when a device is implanted into the full thickness of the skull. All treatments are limited and outcomes vary. The LIFUS device was developed to treat temporal lobe epilepsy. Thus far, investigators have addressed translational challenges and safety.

Bin He from Carnegie Mellon University described electrophysiological source imaging to guide tFUS neuromodulation. A significant correlation was found between unfolded protein response factor (UPRF) proteins and excitatory neurons, which could be a fruitful line of investigation. Next steps include working on mechanisms and also on human trials. FUS might also be used to treat chronic pain.

Jamie Tyler, co-founder of IST (isensetec.com), gave an example of a small business initiative that has advanced research on low-intensity, low-frequency pulsed ultrasound to modulate brain activity. The process yields high spatial resolution afforded by current noninvasive brain stimulation methods. When you do not heat the brain, you can map the brain. A collaborative effort was used to develop standardized techniques for the NeuroFUS system. Small business can benefit from collaborative projects because groups can be leveraged. They should have an established working group to address key gaps, treatment parameters, and safety measures.

Greg Clement from the U.S. Food & Drug Administration, Office of Science and Engineering Laboratories (OSEL), described regulatory research and tools relevant to ultrasound neuromodulation. OSEL has ongoing efforts with better and better-characterized ultrasound abilities and has a role in the regulatory review process. The Medical Device Development Tools program devised the 3-D mechanically accurate brain bio-reactor (now used for BBB modulation, but may be applied to other aspects). Ultrasound safety has no consensus standards (lexicon, characterization, reporting, etc.). Investigators should feel free to contact the FDA.

Pamela Scott from the U.S. Food & Drug Administration, Neurostimulation Devices Psychiatry Branch, discussed regulatory pathways for investigational devices. The Investigational Device Exemption (IDE) regulates submission that permits clinical investigation of devices. IDE approval is needed when the device is a significant risk device as defined by the FDA, for use to support or sustain human life, or of substantial importance in diagnosing, curing, mitigating, or treating a disease. The FDA's decision is final as to whether the device is a significant or nonsignificant risk to the health, safety, or welfare of the subject. The target population, target location, and how the device will be used need to be considered. (The FDA guidance document can be downloaded.)

Pamela Scott, U.S. Food & Drug Administration, Neurostimulation Devices, Psychiatry Branch, explained the regulatory pathways at FDA for investigational devices.

1 Questions to Dr. Bubrick

What about depression and anxiety with epilepsy?

It is very complicated. They are looking at it in their pilot trial.

How do they know when they hit the target tissue after the ultrasound goes through the skull?

A calibrated neuronavigational system determines whether they succeeded.

What about individualizing and optimizing dosage?

Initially we think about things that happened to patients, but that could be different for each person. In epilepsy we look at seizures, which are self-reported. We have to look at this intra-subject for inhibitory vs. excitatory responses. In psychiatry, they are trying to look at genotyping and other factors. We know next to nothing about epilepsy in children. We do only adults in our hospitals, but in other hospitals they treat more aggressively.

2 Questions to Dr. He

Why is the magnetic resonance cholangiopancreatography for sham treatments so small?

We are estimating the neuronal activity induced by the neurostimulation, which is statistically significant among various groups. Source imaging may be applied to focus on a target and distinguish it.

What is the rationale for using treatment for chronic pain? And what about a wearable device?

Imaged neural networks are associated with pain, and current thinking is that it may be possible to develop a wearable device, but it would be a great challenge. So they are developing a helmet so the patient can receive treatment at home.

What about something implanted on the skull? Equivalency between animal and human models? Dose/response relationship?

We have a phantom model, a computational model across the skull, which is one way to apply technology to measure electropotential over the skull. With an in vivo animal model and a human pilot model, we can estimate the strength of the source.

3 Questions to Dr. Tyler

What about NIH approval? What is the difference between venture capital, NIH, and FDA perspectives? Can they collaborate?

We would like to see venture capitalists come in to a project earlier than later. One advantage is secure reimbursement. Now that transcranial magnetic stimulation is reimbursed, it opens a new level. NIH has the ability to collaborate with other agencies, e.g., the Department of Defense, but they rely on milestones and deliverables rather than hypothesis-driven outcomes. It goes back to the concept that you can work together to overcome challenges to achieve the goal.

4 Questions to Dr. Clement

What is the best method to measure pressure in the skull?

Dr. Clement has no preference. He likes to see a worst-case scenario with large and small duration of power. If, for example, temperature increases, testing is needed to know why.

Is there any safety guidance for these much lower FUS doses used in neuromodulation?

Some of this guidance comes from having sufficient data. We would like to see standards compiled by the community as we develop more consensus, e.g., for head phantom so they know labs are comparing the same thing. It would make the process much easier.

5 Question to Dr. Scott

Could you compare ablative treatment vs. gamma knife ablation to treat obsessive-compulsive disorder (OCD)?

We have to go back to the clinical study and see the patient population that was targeted even within OCD, whether it was moderate or severe. Then you consider the most appropriate inputs to monitor it and the endpoints reached.

.

Tuesday,
November 10, 2020

Brain Tumors

Oral Presentation Q&A

Presentations highlighted preclinical studies that investigated the use of focused ultrasound (FUS) alone or with chemotherapeutics in the treatment of brain tumors. Human clinical trials using FUS and microbubbles to open the blood–brain barrier (BBB) and enhance delivery of chemotherapeutics are ongoing.

MODERATORS

Nir Lipsman | Sunnybrook Research Institute

Graeme Woodworth | University of Maryland School of Medicine

SPEAKERS

Cheng-Chia Wu | Columbia University

Focused ultrasound mediated blood-brain barrier opening following radiation is safe in a murine pontine glioma model

Chia-Jung Lin | NaviFUS Co. LTD

Microbubble-facilitated focused ultrasound induces cerebral oxygenation to enhance brain tumor suppressive response in radiation therapy

Christopher Pacia | Washington University, St. Louis

Optimization of focused ultrasound-enabled liquid biopsy (FUS-LBx) in a murine glioblastoma model

So Hee Park | Yonsei University College of Medicine

One-year outcome of multiple blood-brain barrier disruptions with temozolomide for the treatment of glioblastoma

Chenguang Peng | Brigham and Women's Hospital

Perfluorobutane phase shift nanoemulsions-facilitated ablation: A transcranial ablation platform with improved lesion localization and tumor ablation efficiency

Tao Sun | Brigham and Women's Hospital, Harvard Medical School

Focused ultrasound enhances checkpoint blockade immunotherapy for glioblastoma via targeted immunomodulation

Shelly Wang | Nicklaus Children's Hospital

Initial experience with focused ultrasound surgery for central brain lesions in children and young adults

Hong-Jian Wei | Columbia University

Blood-brain barrier opening by focused ultrasound enhances etoposide delivery for glioblastoma treatment

Ko-Ting Chen | Chang Gung Memorial Hospital

Neuronavigation-guided focused ultrasound (NaviFUS) for transcranial blood-brain barrier opening in recurrent glioblastoma patients

1 Question to Dr. Wu

Were any aberrations in brainstem function detected following radiation treatment of the BBB opening, were there any histologic markers of damage, and were there any functional changes such as respiration, cardiac, or other key brainstem functions?

The team was concerned with changes in brainstem function. Both respiratory rate and heart rate were monitored during BBB opening and they did not find any changes. The team was also concerned with the ability to swallow, so they monitored weight changes in the mice as a surrogate marker and also found no change. Regarding histological changes, the tumors had half microhemorrhages and half infiltrative disease. Two pathologists who were blinded to treatment found no differences in pathology between treated and untreated mice.

2 Question to Dr. Park

Please clarify the timing of BBB opening following temozolomide administration, and what was the duration of BBB disruption?

The BBB opening was performed following the first or second cycle of temozolomide, and the BBB was opened with a 1-second burst.

3 Question to Dr. Wei

Please confirm the fact that sonications were being performed at multiple time points because the brain did not show enhancement in T1. How did drug delivery compare within the tumor versus the peritumor space with surgical resection before FUS effect?

The model is attempting to model the clinical experience where FUS is performed following surgical resection of the tumor. The biggest limitation for glioblastoma (GBM) is not disrupting the tumor mass itself, it is destruction of the surrounding tissue to stop microscopic spread. This area has a relatively intact BBB. The researchers aim to treat the tissue that directly surrounded the tumor with FUS, as this area has remaining tumor cell infiltrates, to increase drug penetration.

4 Question to Ms. Lin

What is the optimal time to pair FUS-mediated BBB disruption and radiation? Is there a therapeutic window for this combination?

The optimal window is 2 hours between FUS-mediated BBB disruption and radiotherapy. Prior research suggested that radiotherapy should follow BBB opening as soon as possible

5 Question to Dr. Wang

Please describe the technical parameters for the ablative procedure for hamartomas in the hypothalamus and describe any challenges encountered during these procedures.

For the five patients with hamartomas, there were no specific challenges even in heavily pretreated patients. However, there was one patient with a subependymal giant cell astrocytoma with calcifications that produced challenges during the procedure. The goal of treatment was tumor control, but the tumor increased in size following the procedure.

6 Question to Mr. Pacia

Please describe the earliest and latest time points that FUS-related tumor biomarkers were collected.

The earliest blood sample was collected 10 minutes following the FUS procedure because the MRI was performed to verify the BBB opening prior to blood sample collection. The latest sample was collected at 60 minutes post-FUS treatment. The biomarker concentrations peaked at 10 minutes, or perhaps earlier. This might be due to the short half-life of the biomarkers in blood circulation.

7 Question to Dr. Sun

What are the benefits of the 005 GBM mouse model compared with the GL261 mouse model?

The team found published research suggesting that 005 cells were more similar to humans with regard to the immune profile compared with GL261. GL261 tumors have more T cells and fewer antigen-presenting cells, and GL261 cells are more likely to respond to checkpoint inhibition.

8 Question to Dr. Sun

Has optimal timing for FUS has been determined, given that the checkpoint inhibitor may not need to get into the tumor to have an effect. Is it a drug delivery or immunomodulation challenge?

The team has performed experiments to look at the optimal timing of FUS. Timing seems to matter, but tumor stage is also important.

9 Question to Dr. Peng

What are the differential characteristics between the phase shift nano-emulsions and the commonly used microbubble formulations?

Nano-emulsions are precursors to microbubbles. For nano-emulsions, the perfluorocarbon has a shorter chain, has an increased volatility, and is easily vaporized to a microbubble. The benefit of the nano-emulsion droplets are that they are only activated at the highest-pressure points creating localized damage and are very useful for brain applications. Using these droplets, a higher pressure can be applied directly at the tumor because it is very localized and liquefies the tumor. Whereas, with microbubbles, the damage is limited to the blood vessels.

10 Question to Dr. Park

Regarding a patient who underwent surgery and the resulting pathology results: What is the role for FUS in the treatment of GBM, and what are the next steps for the field?

The pathology report only stated the presence of tumor cells. Temozolomide can partially cross the BBB; the next step will be to look at chemotherapies that cannot pass the BBB.

11 Question to all

Please give a brief summary of the next steps for FUS.

Dr. Peng: Immunotherapy is exciting.

Dr. Wu: The ability to find a chemotherapy that will work in the setting of GBM would revolutionize the field.

.

Brain Tumors

Panel

MODERATOR

Jason Sheehan | University of Virginia

PANELISTS

Adam Sonabend | Northwestern University

Use of ultrasound-based BBB opening for delivery of cremephor-free paclitaxel, from bench to bedside

Francesco Prada | Fondazione IRCCS Istituto Neurologico

Sonodynamic therapy for brain tumors

Hao-Li Liu | National Taiwan University

Evidence of focused ultrasound BBB opening to trigger anticancer immune response

Michael Lim | Stanford University

Focused ultrasound and immune modulation

Hong Chen | Washington University in St. Louis

Sonobiopsy for noninvasive diagnosis of brain tumors

Adam Sonabend discussed recent clinical data from the SonoCloud 2nd generation device with 9 ultrasound emitters. A phase 1/2 clinical trial of BBB disruption with this device to enhance paclitaxel delivery in recurrent glioblastoma recently started in the US and is enrolling patients.

Francesco Prada discussed research using low-intensity focused ultrasound in combination with sensitizing agents, known as sonodynamic therapy. Published and ongoing studies confirm the potential of sonodynamic therapy as an emerging technique in the field of neurosurgery. 5-aminolevulinic acid (5-ALA) was previously demonstrated to be a sonosensitizer. Sonodynamic therapy offers the possibility to treat brain tumors in a harmless, noninvasive, and site-specific way.

Hao-Li Liu described preclinical research with C6 glioma cells and FUS-BBB opening could trigger an immune response by recruiting CD8+ T cells.

Michael Lim discussed preclinical studies and found that various immunotherapy treatments could act synergistically with stereotactic radiosurgery to improve overall survival. This research led to a phase 1 clinical trial combining TIM-3, PD-1, and stereotactic radiosurgery. Preclinical research also demonstrated that local chemotherapy enhanced immunotherapy, but systemic chemotherapy did not have the same effect.

Hong Chen discussed the SonoBiopsy technique for blood-based diagnosis. FUS-BBB opening enables two-way transfer across the BBB. Feasibility was demonstrated in both small (mouse) and large (pig) animal models. SonoBiopsy could provide complementary diagnostic information in place of invasive biopsies.

1 Questions to Dr. Sonabend

For the SonoCloud device, how many of the nine transducers were activated during treatment?

All 9 transducers are activated at the same time. In a prior clinical trial, the transducers were turned on in an escalating cohort, leading up to the final cohorts being treated with all 9 transducers.

Are there future plans to make larger devices with more than 9 transducers?

The SonoCloud 9 is already a technological advancement. The device can treat patients without MRI guidance, sonication area is very broad, and sonication can be carried out in a short period of time (~4 minutes), which are all advantages. The ability to target the peritumoral area is adequate for this approach. It can also be done in an infusion suite on an out-patient basis.

2 Question to Dr. Liu

Why did the higher mechanical index (MI) have a greater immune response, and please describe the pulsing parameters?

Previous research suggested that lower FUS exposures were not enough. The rate of lymphocyte infiltration was correlated with the FUS-exposure level. Higher pressures can cause red blood cell extravasation. The team has yet to identify the exact cell types that infiltrate the tumor, but they think that the cells are CD8+ T cells based on preclinical data.

3 Question to Dr. Chen

Regarding SonoBiopsy, what is its potential to enhance the opening of the already defective BBB around tumors in the brain for biopsy?

The technology for SonoBiopsy is not different from opening the BBB for drug delivery. The technology has built on the opening of the BBB to introduce the concept of opening the BBB to release brain-tumor-specific biomarkers from the brain to the blood. Research had already shown that the BBB could be opened pretty much anywhere in the brain and near tumors. Compared with other blood-based biomarker assays, SonoBiopsy allows the researchers to pinpoint specific brain areas to obtain biomarkers. This assay is meant to be a replacement for tissue obtained through biopsy.

4 Question to Dr. Lim

What are the technical challenges and opportunities for the clinical use of FUS for BBB opening and treatment with immunotherapy?

The FUS allows the precise application of immunotherapy to a targeted location in the tumor. It might also depend on the type of immunotherapy that the clinician would like to use; small-molecule inhibitors do not easily cross the BBB. However, some of the checkpoint inhibitors cross the BBB and the antigen presentation occurs outside of the brain in the cervical lymph nodes. In this case, FUS could be used to maximize the delivery of the drug and antigen presentation.

5 Question to Dr. Prada

Please clarify the difference between 5-ALA and fluorescein in terms of the incubation time and killing effect.

5-ALA and fluorescein are different in how they accumulate in the tumor. 5-ALA accumulates in the tumor cells, and fluorescein accumulates in the extracellular space. Both compounds generate free radicals from the interaction between the sensitizer and ultrasound; they also both cause apoptosis and necrosis. Preclinical in vitro research suggested a small induction of necrosis and apoptosis with ultrasound alone. Dr. Prada postulated that the sensitizers may enhance the effects of ultrasound.

6 Question to Dr. Prada

Could sonoluminescence activate sonosensitizers to generate free radicals for tumor eradication?

Dr. Prada responded that this could be a potential mechanism of action

7 Question to Dr. Lim

Was there sufficient penetration of checkpoint blockade to tumor cells when there is only non-enhancing tumor remaining after resection?

This is unknown. Dr. Lim hypothesized that checkpoint inhibitors are able to traverse into non-enhancing tumor tissue. Penetration is probably decreased because there are fewer immune cells present. There was discussion that tumors are heterogeneous and as the technology improves, different areas of the tumor may be targeted with different treatments.

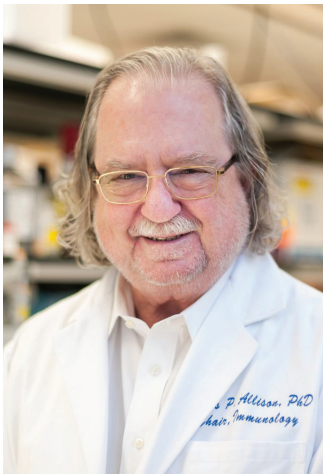
.

Keynote Speaker

James Allison, MD

Anderson Cancer Center

Co-winner, 2018 Nobel Prize in Physiology or Medicine



James Allison, MD

In his address titled “Immune Checkpoint Blockade in Cancer Therapy: New Insights into Therapeutic Mechanisms of Anti-CTLA-4 and Anti-PD-1,” Dr. Allison provided background information on his discovery of the immune checkpoint blockade and then described recent research to extend the therapy to more types of cancer and increase its effectiveness.

Cytotoxic T-lymphocyte-associated protein 4, or CTLA-4, is an immune cell protein found on T cells that downregulates the body’s immune response; these molecules keep the immune response from getting out of control. To illustrate how blocking CTLA-4 proteins enhances tumor-specific immune responses, Dr. Allison shared a case study of a patient with metastatic melanoma who, after one treatment, experienced complete resolution of two subcutaneous nodules, 31 lung metastases, and a 0.5-cm brain metastasis. Preventing CTLA-4 proteins from slowing the immune system allows the immune system to fight tumor cells.

A second signaling protein on the T cell surface, cluster of differentiation 28, or CD28, helps CTLA-4 proteins work more efficiently, so researchers found that this receptor also needs to be blocked. When CTLA-4 proteins signal T cells to stop working, they prevent the immune system from attenuating or terminating the proliferation of the cancer cells. Blocking CTLA-4 proteins allows the immune system to do its job, and this type of treatment is curative: after the body develops enough T cells to kill a tumor, those T cells stay in the body forever and keep it tumor-free.

Ipilimumab was the first fully human CTLA-4 antibody. It was approved by the FDA in 2011. While it creates objective responses to many types of tumors, it is also associated with serious but generally manageable adverse events and, rarely, autoimmune complications. Unfortunately, ipilimumab did not work for all types of cancers, and it was not equally effective in all patients. Other laboratories investigated additional immune blockade checkpoint proteins and discovered the programmed death 1 (PD-1) molecule. PD-1 has a different mechanism from CTLA-4, wherein the tumor identifies and then creates a molecule that blocks the PD-1 receptors. An anti-PD-1 antibody was successfully developed and tested (nivolumab) in several, but not all, types of cancer.

The next step was combination trials. Anti-CTLA-4 plus anti-PD-1 studies were more successful in treating melanoma but were also successful with previously resistant cancers. Cancers with high rates of somatic mutations have typically had the highest response rate to immunotherapies. Additional antibodies were discovered, and to date, seven immune checkpoint inhibitors have been approved by the FDA.

Dr. Allison and his colleagues have now developed a comprehensive translational immunotherapy program to conduct more clinical trials on larger numbers of patients while

gathering longitudinal biosamples and a high volume of tumor tissue slides. This is a powerful way to use large amounts of data to improve the response rate of checkpoint inhibitors.

Reverse translation of tumor tissue samples is a novel method for choosing treatments based on genomic data. Dr. Allison's group has been studying the characteristics of immunogenic and nonimmunogenic tumors; he provided several examples of turning "cold," or unresponsive tumors into responsive tumors. This work led to a successful combination trial for prostate cancer; however, the toxicities remained high. New combination trials are now seeking to use chemotherapy and genomic analyses to prime the immune system to improve the immunological response of prostate cancer. Other possible combinations include blocking multiple checkpoints, targeted therapies, and radiation therapies.

The immune response is started by priming the tumor. Clinicians should not seek to kill every last tumor cell; instead, they should prepare the immune system to do that. Improving median survival is useful, but the hope is that cancer immunotherapy can move the tail of the curve as high as possible. The more that can be learned about the immune system, the better our chances of achieving the goal of unleashing it against cancer.

• • • • •

Cancer Immunotherapy—Brain

Oral Presentation Q&A

Presentations highlighted the use of FUS in combination with the immune system. Preclinical studies investigated the use of FUS to open the blood–tumor barrier and characterize the immune response as well as in combination with immunotherapy. Human clinical trials using FUS and microbubbles to open the BBB and enhance delivery of chemotherapeutics are ongoing.

MODERATOR

Michael Lim | Stanford University

SPEAKERS

Richard Price | University of Virginia

Immunomodulation of intracranial melanoma in response to blood-tumor barrier opening with focused ultrasound

Natasha Sheybani | University of Virginia

Immuno-PET assessment yields a rational paradigm combining FUS blood brain/tumor barrier disruption with CD47 blockade for glioma therapy

1 Question to Dr. Price

Why did dendritic cells mature in the meninges but not in the lymph nodes or the tumor itself?

The team is not exactly sure. Perhaps there was antigen flow into the meninges, and this did not occur in the other organs. It could also be possible that there is a resident population of dendritic cells in the meninges that are capable of responding to antigen. The meninges environment may have more cytokines and chemokines that promote dendritic cell maturation. The lymph nodes were superficial and the deep cervical lymph nodes could not be analyzed.

2 Question to Dr. Sheybani

How are the antibodies trafficked into the tumors following FUS?

This is an important question that emerged from the study. One hypothesis is that CD47 can promote antibody delivery. They postulate that CD47 antibody combined with FUS may synergize to increase the permeability of the barrier on a longer scale. Contrast-enhancement showed greater leakage of gadolinium from the tumor in the FUS-treated group compared with the CD47 group. Analysis of the immunological sequelae or histology has yet to be carried out, but further insight is needed.

3 Question to Dr. Price

Given the reversal in signal changes at 6 hours versus 24 hours, would repeated treatments make the effect on the inflammatory profile longer lasting?

This was likely, although not the goal of the study. The goal of the study was to use a low level of FUS to open the BBB and look for a sterile inflammation response as well as other downstream immunological sequelae. A higher MI could increase CD8+ T cell infiltration.

4 Question to Dr. Price

What would be the next step toward using this in humans?

There are a lot of opportunities. For example, checkpoint inhibitors are in trials now. Merging FUS with new knowledge of the immune system in the brain is interesting. FUS could be used to move fluid in the brain to the meninges or draining lymph nodes, which would activate the adaptive immune response.

5 Question to Dr. Sheybani

The PET scan showed activity in other parts of the body in addition to the brain.

The analysis was focused on the brain and tumor-bearing regions. They plan to look in the peripheral lymph nodes in the future. Automated gamma-counter measurements did not show any changes peripherally.

6 Question to Dr. Price

Was a dose-response expected between FUS and immunomodulation?

There is a vast perimeter space to be explored. Greater MI, perhaps with histotripsy, would be interesting to look at.

7 Question to Dr. Sheybani

Could the same effect be applied to chemotherapy or other drugs?

Preclinical research had discrepancies on timing of drug administration, whether before or after FUS was better. She cautioned that these results were likely therapy- and pathology-dependent, and possibly model dependent. Timing of when to deliver FUS in combination with immunotherapy is an important consideration going forward.

8 Question to Dr. Price

Have any patterns emerged from bulk sequencing, and was any specific immune cell population predominant?

The next step will be single-cell sequencing. From the bulk sequencing, there were certain cytokines (TNF- α and IL-6) and chemokines identified. H2-K1, H2-D1, MHC-1 transcripts were identified as well. There was no single predominant theme, but that was expected with sterile inflammation.

9 Question to Dr. Sheybani

Regarding the situation where antibody is injected prior to opening the BBB, could this be combined with radiation?

Dr. Sheybani stated that this would likely be beneficial. It is yet to be determined if these results are reproducible with other agents.

.

Cancer Immunotherapy—Breast

Oral Presentation Q&A

MODERATORS

Katherine Ferrara | Stanford University

Craig Slingluff | University of Virginia

SPEAKERS

Parwathy Chandran | National Institutes of Health

Immune cell modulation of pulsed focused ultrasound in murine melanoma and breast cancer models

Clifford Cho | University of Michigan

Non-thermal histotripsy focused ultrasound tumor ablation as a means of generating immunostimulatory tumor vaccines

Gadi Cohen | National Institutes of Health

Temporal immune changes of murine breast and melanoma tumor microenvironments following pulsed focused ultrasound

Patrick Dillon | University of Virginia

PD-1 inhibition to modulate response to FUS in metastatic breast cancer

David Goertz | University of Toronto

Ultrasound stimulated microbubbles enhance the potency and durability of anti-PD-L1 checkpoint blockade therapy in an orthotopic breast tumor model

Natasha Sheybani | University of Virginia

Combination of thermally ablative focused ultrasound with gemcitabine controls breast cancer via adaptive immunity

1 Question to Dr. Chandran

Is there a hypothesis to explain why some tumor lines revert back to a cold phenotype following partial FUS, while others do not?

It is likely because of tumor heterogeneity as melanoma and breast cancer have different cells of origin. FUS also likely modulates the tumor microenvironment (TME) in different ways. In melanoma the tumors shifted from a cold to a hot TME.

2 Question to Dr. Chandran

What are the implications regarding the fact that the changed gene pathways are not classically associated with immune activation?

There is no clear answer, as analysis is ongoing. This is likely due to the innate differences in the individual TME. For example, in the B16 cell line, there was an anti-tumorigenic effect along with upregulation of immune responses.

3 Question to Dr. Cohen

About Ki-67 expression after partial FUS, did the changes occur in tumor cells or immune cells?

This was in tumor cells, and he theorized that this was a compensatory response

4 Question to Dr. Cohen

Concerning the differences in mechanical properties of various tumor cell lines that result in quick translation of the tumor by radiation forces so that the tumor quickly moves out of the focal zone: This results in differences in the delivered thermal or mechanical doses. Is this a concern?

This is a concern. The different delivered doses are unknown, it could even be a result of genetic properties or the structure of the cells themselves. This is currently under investigation.

5 Question to Dr. Cohen

About 4T1 suppressed genes resulting in an immunosuppressive environment: Were there any particular genes that stood out with regard to the 4T1 cells or immune cell types?

There are four main pathways in the genes that were analyzed. One pathway was the mesenchymal to endothelial cell transfer, which is related to drug resistance.

6 Question to Dr. Dillon

What factor is the most strongly influenced patient response: previous treatment, receptor status, or some other factor?

There is no definitive answer yet, as the trial is ongoing. Preliminary data suggest that patients with limited amounts of prior treatment would be more likely to have an immunologic response as there is not as much immunologic exhaustion from heavy prior treatment. He also speculated that younger patients may have better immunologic responses.

7 Question to Dr. Dillon

About changes in immune cell infiltrates appearing to be less consistent and less dramatic than changes in RNAseq data: What might be driving those changes? The changes observed are similar in the ablated and peri-ablated regions: Was there any hypothesis as to why this occurred?

The hypothesis was that there would be dramatic changes in the immune microenvironment in the ablated area compared with the peri-ablated area because of a lack of tumor necrosis in the peri-ablated area. The actual results were confusing, and analysis is not yet complete. However, perhaps there is difficulty differentiating the two zones or perhaps there are no differences. Future research will make sure that the two areas are well-defined and look at differences in the immune cell populations.

8 Question to Dr. Goertz

Does vascular disruption enhance the effects of chemotherapy and immunotherapy? However, other research has shown that lower oxygen levels are detrimental to maximizing radiation effects. Why would lower oxygen levels enhance the effects of immunotherapy and enhance the effects from radiation?

Prior research with vascular disruption agents combined with chemotherapy hypothesized that vascular disruption would help the action of chemotherapy. The center of the tumor undergoes necrosis, but not the periphery. The hypothesis is similar here that vascular disruption could potentiate immunotherapy.

9 Question to Dr. Goertz

Are there proposed mechanisms of FUS microbubble treatment that could potentiate the response to chemotherapy plus anti-PD-1?

There is a spatial component. A previous experiment with subcutaneous colorectal cancer cells did not find changes in T cell populations in the tumor, except modest changes in T-helper cells. In the current experiment they were unable to perform flow cytometry due to too much necrosis. They are currently performing abscopal studies to look at flow cytometry and T cell populations.

10 Question to Dr. Sheybani

About the use of gemcitabine: Are there data on the depletion of myeloid-derived suppressor cells, and was there enhancement of tumor-reactive T cells.

The study was based on prior research that showed transient depletion of myeloid-derived suppressor cells and enhancement of functional CD8+ T cells. Flow cytometry from the current study found a sustained increase in CD8+ T cells and CD44+ T cells in mice treated with gemcitabine as well as those also treated with FUS. Data on the myeloid-derived suppressor cells were recently published in the *Journal of Immunotherapy for Cancer*.

11 Question to Dr. Chandran

Do cytotoxic T cells, F4/80 cells, and M1 cells in the spleen and lymph nodes on day 1 after partial FUS transform the tumor into a hot tumor on day 3?

This is a strong innate response. Both innate and adaptive immune responses are engaged in the antitumor response.

.

Cancer Immunotherapy—Other

Oral Presentation Q&A

MODERATORS

Katherine Ferrara | Stanford University

Craig Slingluff | University of Virginia

SPEAKERS

Harshini K. Ashar | Oklahoma State University

Immunological and therapeutic effects of focused ultrasound in canine cancer patients

Lynn T. Dengel | University of Virginia

Pilot evaluation of focused ultrasound ablation and focused ultrasound ablation plus PD-1 antibody blockade in advanced solid tumors

Avinash Eranki | Indian Institute of Technology, Hyderabad

Immune sensitization and therapeutic impact of boiling histotripsy in refractory murine neuroblastoma
Temporal dynamics of intratumoral immune cell infiltration triggered by boiling histotripsy

Cécile Fant | INSERM

Impact of a combined immune checkpoint inhibitor and mechanical focused ultrasound treatment in a MC38 preclinical model

Ashish Ranjan | Oklahoma State University

Can focused ultrasound enhance the immunogenic properties of doxorubicin and ThermoDox in preclinical and clinical settings?

Mohit Pratap Singh | Albert Einstein Cancer Center

Boiling histotripsy and CD40 activation re-sensitize the immunologically “cold” tumor to checkpoint blockade therapy

Caitlin Tydings | Children’s National Hospital

High intensity focused ultrasound thermal ablation in combination with checkpoint inhibitors for the treatment of refractory murine neuroblastoma

1 Question to Dr. Ashar

Were there any adverse events or off-target impacts on the 50%-to-60% regimen, and did this vary with tumor type?

Because the area of treatment was small, there were few observed side effects outside of skin discoloration. This varied by tumor type; highly vascularized tumors had greater skin discoloration.

2 Question to Dr. Ashar

Were there any challenges with the setup, and whether there was difficulty reaching a particular tumor or the ability to maintain anesthesia?

Tumors close to the skull or ribcage and topical tumors were excluded from the procedure.

3 Question to Dr. Dengel

Were there any reasons to exclude patients based on immunologic status or tumor location?

All patients get an ultrasound prior to treatment that allows assessment of the tumor for FUS parameters and positioning of the patient. Only 33% of the tumor volume is treated, which helps with rapid treatment. The treatment is well tolerated with minimal sedation.

4 Question to Dr. Dengel

How do you plan to account for different cancers responding to FUS in various ways, and how to differentiate between responders and non-responders?

Because this was a pilot study, they cannot answer these questions. Given the diverse patient population, it would be difficult to draw firm conclusions on the different tumor types. The primary goal of the study is to look at safety and at CD8+ T cell infiltration into the tumor. This pilot study will help to inform future studies.

5 Question to Dr. Eranki

Did you look at chronic time points to understand if the T cell response was sustained within a relative window of adaptive immunity?

In this study, only three time points were assessed. Investigating chronic time points is currently underway. Understanding this is key to delineating the adaptive response that is either pro- or anti-tumor.

6 Question to Dr. Eranki

Why was there a dynamic difference between CD4+ and CD8+ T cells at 1 day after boiling histotripsy and then returns to baseline levels?

The stain used in the study did not differentiate T cell activity. They hypothesized that figuring out the long-term effects will help determine the kinds of T cells and pathways that are involved.

7 Question to Dr. Fant

Please discuss the data regarding FUS first versus PD-1 first and the success for immunomodulation.

Dr. Padilla answered for Dr. Fant: There were three sequences (FUS first, PD-1 first, and both at the same time). There was better tumor growth control and overall survival with FUS first, but it also occurred with PD-1 first.

8 Question to Dr. Padilla

Was there a specific protocol going forward based on these findings?

There is no clear mechanistic understanding of why starting with FUS is better. The general hypothesis is that it is better to activate the tumor before treating with PD-1.

9 Question to Dr. Ranjan

Do you have a hypothesis for the drop-off in regulatory T cells following FUS treatment and the restoring of these levels to baseline within 7 days?

The reason is unknown. It is likely a compensatory mechanism.

10 Question to Dr. Ranjan

What frequencies were used and what method was employed to cool the mouse?

Coupling in a water tank was done to control temperature; the mice lost body temperature but recovered well after the procedure. The objective of the study was to look at whether locally administered doxorubicin was better for a systemic immune response.

11 Question to Dr. Singh

About the choice of intra-tumoral CD40: Were other routes of administration considered, and were researchers concerned with interactions with dendritic cells in the lymph nodes?

Prior research showed that systemic administration of CD40 caused liver toxicity. They chose to administer CD40 intratumorally to bypass liver toxicity. Additional research showed that this route of administration did not cause liver toxicity.

12 Question to Dr. Tydings

How was temperature assessed and monitored during the treatment?

Preliminary work with phantoms helped to determine the temperature. They were unable to measure temperature in real time.

13 Question to Dr. Tydings

Can PD-1 be a marker of T cell activation or exhaustion and was this evaluated?

Staining was done for general T cell expression and Ki-67 for T cell replication, but they did not look at T cell function. The only time points measured were 24, 48, and 72 hours post-treatment.

14 Question to Dr. Singh

Did the soluble CD40 molecule remain local or did it diffuse?

They did not evaluate this. Previous research suggests that it diffuses out of the tumor.

15 Question to all

What makes a mouse study successful?

Dr. Padilla: The first goal is to achieve a complete response and study the immune infiltrate after that has been achieved.

.

Cancer Immunotherapy

Panel

MODERATOR

Jill O'Donnell Tormey | Cancer Research Institute

PANELISTS

Teresa LaVallee | Parker Institute for Cancer Immunotherapy

Mechanism of immune modulation for science driven IO combinations

Kathy Ferrara | Stanford University

FUS ablation and combination protocols

Zhen Xu | University of Michigan

Histotripsy tumor ablation-mediated immune stimulation

Natasha Sheybani | Focused Ultrasound Foundation, Stanford University

Ushering FUS into the era of precision immuno-oncology

Lynn Dengel | University of Virginia

Investigation of focused ultrasound ablation as a mechanism to enhance systemic immune therapy in advanced solid tumors

Teresa LaVallee described the work of the Parker Institute for Cancer Immunotherapy. Their research strategy is to perform deep tumor sequencing along with immune profiling to learn more about treating cancer.

Kathy Ferrara from Stanford University discussed FUS ablation and combination protocols with immunotherapy. The timing of FUS versus immunotherapy is important and research has shown that immunotherapy before FUS blunts the protumor inflammatory response. Magnetic resonance-guided FUS (MRgFUS) ablation leads to sustained debulking of the tumor and an enhanced therapeutic accumulation.

Zhen Xu from the University of Michigan discussed histotripsy, which is nonthermal and nonionizing and uses cavitation to mechanically disrupt cells without denaturing the protein. Histotripsy liquefies the tumor and releases immunogenic tumor antigens that act as immunoprotective vaccines. Histotripsy also has an abscopal effect and inhibits the growth of distant and untreated tumors. Preclinical work shows that histotripsy enhances immune checkpoint inhibitor administration.

Natasha Sheybani from Focused Ultrasound Foundation, Stanford University, discussed key challenges and considerations concerning FUS and immunotherapy combination treatment. The diversity of intra- and antitumor heterogeneity can impede efficacy. Clinical studies and endpoints for immunotherapy treatment are distinct from conventional therapy. The timing of FUS and immunotherapy are also important considerations. Lastly, biomarkers for safety and efficacy are needed. Dr. Sheybani also encouraged participants to look into FUS foundation resources for immunotherapy.

Lynn Dengel from the University of Virginia presented the trial design for a study of FUS in combination with PD-1 blockade. For FUS treatment, the researchers chose a single treatment over a 5-to-10 mm diameter; treatment would be applied to 33% of estimated tumor volume. Primary endpoints are safety and toxicity as well as measuring CD8+ T cell infiltration in treated and untreated metastasis and other immunologic endpoints. The trial is open and currently enrolling patients.

1 Question to all

What should be measured in order to better understand the mechanistic action of FUS on the immune system?

Dr. Ferrara: Measuring temperature, pressure, distribution, and timing are important. Without measuring temperature and pressure, it can be difficult to replicate experiments. Next, measure tumor cell death to identify therapeutic penetration and tumor-antigen presentation on myeloid cells, dendritic cells, and macrophages within the tumor, lymph nodes, and systemically. Measuring cytokine response to see if a viral response occurred is also important.

Dr. LaVallee: It is important to think about the question and not the specific assays, etc. A holistic view to define the mechanism of action, key cell types, and kinetics will help to design thoughtful clinical trials and may also help optimize patient selection. Clinical studies should perform broad tumor profiling with whole exome sequencing, RNAseq, and TCRseq at both baseline and following treatment. Creating a tissue bank with archival baseline tissue will help to create a database to look for changes. It is also key to understand the players involved in activating T cells and T cell fitness. Since tumor biopsies are not amenable to longitudinal study, blood-based biomarkers are key to observing different sets of immune cells over time. She also emphasized the importance of using proteomics to identify and analyze cytokines and chemokines in the blood.

2 Question to Dr. Dengel

Can you define the optimal schedule for biopsies?

The current trial looks at 24 and 36 hours post-FUS. It is key to determine the optimal time for biopsies in order to catch the key changes occurring. Liquid biopsies are more feasible, but determining the right schedule is ongoing.

Dr. Xu: Timing of biopsies may depend on the FUS modality. For thermal ablation, the immune response occurs rapidly following treatment. For histotripsy, or a mechanical approach, immune response increases over the span of 7 to 10 days. Cellular debris is reabsorbed by the body along with a continued systemic response for several weeks. Preclinical research is important to guide the clinical trial design on timing.

3 Question to all

What is the optimal timing for the inclusion of imaging in looking at the interplay of the immune system and FUS?

Dr. Sheybani: Different imaging modalities can be used both clinically and pre-clinically in place of biopsy. For example, the distribution of biomarkers that are predictive of tumor

response to immunotherapy, tracking different immune cells, or immune-related toxicity can be answered with imaging modalities. Recent technological advancements have been with molecular imaging that allows this exploration. There is a need for better approaches for predicting response that will allow the leveraging of more sophisticated techniques, such as radiomics, to improve the treatment of patients in the clinic.

4 Question to all

How should the type of FUS be selected to combine with a given immunotherapy?

Dr. Sheybani: The choice of FUS will depend on the ultimate goal. Preclinical studies of FUS for barrier disruption with GBM have also led to previously unknown immunological effects.

Dr. Ferrara: There are a lot of choices. It is also important to further characterize the immunological effects of the available immunotherapy agents to better inform the choices. The immunotherapy choice should be based on organ or molecular-specific signatures, even in the absence of FUS. Right now, FUS is dictated by location of the tumor. There are clinical systems that can disrupt the BBB and systems that can be combined with drug delivery, but better FUS tools may be developed in the future.

5 Question to all

What is the strategy for making a rational design of FUS and immunotherapy combinations?

Dr. Ferrara: One strategy is to just aim for killing tumor cells, and using a blunt effect may also be very effective.

[The session ended, and Dr. Ferrara did not have time to elaborate.]

• • • • •

Fireside Chat

Cancer Therapy *Beyond Ionizing Radiation*



Chandan Guha, MBBS, PhD



Samuel Hellman, MD

Chandan Guha, MBBS, PhD, from the Albert Einstein Cancer Center sat down with **Samuel Hellman**, MD, from the University of Chicago to discuss the future of cancer therapy beyond radiation. Dr. Hellman, who was trained as a radiation oncologist, has been treating patients with cancer since 1960. “To me,” said Dr. Hellman, “the most interesting part of clinical treatment was the puzzle of cancer, and that was why I became involved.”

After training at Yale and the Royal Marsden Hospital in London, Dr. Hellman started the radiation oncology department at Harvard Medical School, which served all of the regional hospital systems—many of which later merged. After 15 years, he moved on to become chief of service at Memorial Sloan-Kettering Cancer Center before becoming the Dean of the Medical School at the University of Chicago.

In 1995, Dr. Hellman and colleagues wrote an influential editorial in the *Journal of Clinical Oncology* on the concept of oligometastases. His primary interest at that time was the natural history of disease, especially for breast cancer. He collected data from patients at both Memorial Sloan-Kettering and the University of Chicago, analyzed them to discover that the size of the cancer affected the rate of metastases, and concluded that clinical breast cancer evolved: the tumor becomes more malignant as it grows and more efficient in spreading. That conclusion led Dr. Hellman and his colleagues to believe that there was an intermediate state between local and widespread metastases. They went on to conduct molecular and biological studies to verify the evolution of the disease and how it metastasizes.

The two physicians discussed how the important immunological effects of ionizing radiation can now be further exploited. These effects are becoming more understandable and controllable. Removing a tumor with surgery also removes its antigens, but the antigens are needed to activate the immune system. Focal adjuvants are also important to maintain when using ablation therapies such as focused ultrasound. While ionizing radiation can also inhibit the immune response by destroying circulating lymphocytes and regional lymph nodes, focused ultrasound does not do this.

Dr. Hellman became interested in focused ultrasound by chance. In the late 1960s, he met researchers at General Electric who were splitting off therapy from diagnostics. They suggested that Dr. Hellman join the board for the therapy group, which he did. When they made enough advances to provide therapy through the skull, Dr. Kassell also joined the board.

To Dr. Hellman, focused ultrasound showed much promise, especially for use in the abdomen. At a time when treating lung and brain tissues seemed out of reach, and with accuracy as a question, uterine fibroids were a good place to start. Integrated therapy

always made sense to Dr. Hellman, and he wanted to integrate focused ultrasound with all of the focused energies. He has always advocated for a collaborative rather than competitive role between therapies because it doesn't make sense for patient care to transfer patients from one treatment area to another. Dr. Hellman said that Ferenc Jolesz, who was one of the intellectual founders of focused ultrasound, always wanted an operating suite with no operating. Dr. Hellman's guidance in the early days of focused ultrasound has been incredibly important and influential.

.....

Special Lecture

Focused Ultrasound and Liquid Biopsy in Brain Tumors *A Critical Role for the Blood-Brain Barrier?*



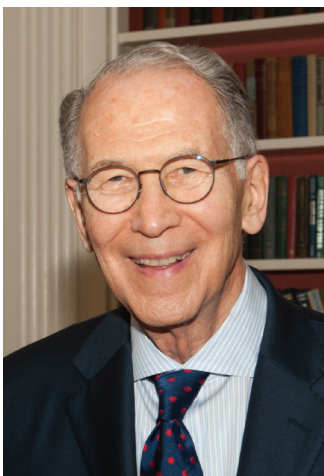
Chetan Bettegowda, MD, PhD

In this special lecture, two neurosurgeons, **Chetan Bettegowda**, MD, PhD, from the Albert Einstein Cancer Center sat down with **Samuel Hellman**, MD, from the University of Chicago to discuss the future of cancer therapy beyond radiation. Dr. Hellman, who was trained as a radiation oncologist, has been treating patients with cancer since 1960. "To me," said Dr. Hellman, "the most interesting part of clinical treatment was the puzzle of cancer, and that was why I became involved."

Liquid biopsy is superior to a standard biopsy in terms of time needed, completeness of molecular tissue capture, ease in obtaining, lower risk, and noninvasiveness. Liquid biopsy can provide early detection, continual monitoring, and detection of recurrence or treatment-resistant mutations of cancerous tumors. There have been many recent developments in the field of liquid biopsy, especially for detecting circulating cell-free DNA. Sensitive technologies are needed to identify tumor-derived circulating DNA, an application of personalized medicine.

Patients with glioblastoma (GBM) experience invasive recurrence after tumor resection, chemotherapy, and radiation. This is a critical clinical problem. Using focused ultrasound to open the BBB before or after surgical treatment of GBM may provide new solutions. Two clinical trials are underway at the University of Maryland. One trial uses focused ultrasound to open the BBB prior to surgical resection; the other opens the BBB after surgical resection but prior to chemotherapy administration. Researchers are particularly interested in determining whether opening the BBB with focused ultrasound might allow larger quantities of circulating tumor DNA to enter the bloodstream. Drs. Bettegowda and Woodworth recently received NIH funding to conduct such a study. Their initial work will target unresectable thalamic gliomas, low-grade gliomas, and aggressive glioblastomas.

.....



Samuel Hellman, MD

Special Session

International Society for Therapeutic Ultrasound (ISTU)

Because ISTU was forced to cancel their 2020 annual meeting, the Focused Ultrasound Foundation was able to dedicate an afternoon to this partner organization.”

Updates and Introduction

Joo Ha Hwang, MD, PhD, from Stanford University provided several society updates and introduced the 2020 Lizzi Award Winners: **Hong Chen**, PhD, and **Meaghan O'Reilly**, PhD. Each scientist presented their groundbreaking work.

2020 Lizzi Award Presentations

- *Focused Ultrasound-Enabled Two-Way Transfer across the Blood-Brain Barrier*
Hong Chen, Washington University in St. Louis
- *Transvertebral Ultrasound for Targeted Therapy in the Spinal Cord*
Meaghan O'Reilly, Sunnybrook Health Sciences Centre

Remembering Charles Cain

A Pioneer and Leader in Focused Ultrasound

Zhen Xu, PhD, from the University of Michigan, presented a personal and touching tribute to the life and work of Professor Charles Cain, a pioneer in the development of focused ultrasound histotripsy.

.

Wednesday,
November 11, 2020



Michael Milken

Keynote Speaker

Michael Milken

Milken Institute

As he does at each global event that he hosts, Mr. Milken began his address by reminding the audience that the extension of human life has been dramatically improved over the past 120 years due to improvements in sanitation, the development of antibiotics, the implementation of vaccines, progress against heart disease, and investment in bioscience research. These advances have driven as much as 50% of the world's economic growth over the past 200 years. Bioscience is more than health: it includes abundant food, clean water, defense against pandemics and bioterrorism, reliable energy supplies, and environmental sustainability.

With the implementation of modern capital markets over the past 50 years in the United States, the growth of new industries and technologies through small- and medium-sized businesses led to the creation of nearly 62 million jobs in the private sector. Looking forward, the 21st century is being defined by worldwide competition for talented human capital. Human knowledge, experience, and expertise drive the value of technology today.

Philanthropists took the early risk on funding medical innovation and technology. They found that focused collaboration and investment in young people with new ideas created greater returns. Technological advances over the last 40 years can be attributed to cost, speed, data storage, and access. Antiquated infrastructure prevents science from moving forward at a speed that it is otherwise capable of.

Over the past seven years, the field of focused ultrasound has experienced tremendous growth in its clinical indications, device manufacturers, mechanisms of action, research sites, and treatment centers. Mr. Milken recalled an episode of Star Trek when Dr. Bones went back to Earth to find that medicine had not progressed. Cancer treatments—especially for prostate and melanoma—have, however, made significant progress and extended life expectancies.

The COVID-19 pandemic has further unveiled the fact that medical care is not available to everyone. In response, the Milken Institute created a six-point call to action that included education, testing, prevention, treatment, cure, and financial assistance. Mr. Milken also recorded more than 100 podcasts on the topic of “Leadership in a Time of Crisis” to provide everyone the same level of access to the best information about life during the pandemic. The level of collaboration, including opening patent libraries and waiving royalties, to create and test vaccines to address this pandemic has been truly astounding. This is what is needed to advance medicine at the speed of life. Telemedicine has become the medicine of the future.

In summary, the long-term stimulus is the people who work in bioscience. Baseball legend Jackie Robinson said, “A life is not important except in the impact that it has on other lives.” Focused ultrasound will change the world for billions of people, extend the length, and improve the quality of life.

.....

Breast Cancer

Panel

MODERATOR

Suzanne LeBlang | Focused Ultrasound Foundation

PANELISTS

Frédéric Padilla | Focused Ultrasound Foundation

Use of ultrasound-based BBB opening for delivery of cremephor-free paclitaxel, from bench to bedside

Allison Payne | University of Utah

Breast MRgFUS first-in-human clinical trial technical evaluation

Chrit Moonen | University Medical Center, Utrecht

MR-HIFU in Breast Cancer: Clinical Trials at Utrecht

David Brenin | University of Virginia

FUSA for Tumors in the Breast at UVA

Manon Braat | University Medical Center, Utrecht

Frédéric Padilla from the Focused Ultrasound Foundation presented methods to perform real-time visualization of the treatment volume and monitoring using MR-guided systems, ExAblate 2000 (Insightec, Israel) and Sonalleve (Profound Medical, Canada). This demonstrated the efficacy of high-intensity focused ultrasound (HIFU) ablation for fibroadenoma and breast cancer. Clinical outcomes were encouraging, and the treatment should equal to surgery. In a case study, when HIFU was combined with immunotherapy, 10-month follow-up showed complete remission. Clinical trials are ongoing. Challenges include: competing approaches, treatment time, technological challenges, and mechanisms of action.

Allison Payne from the University of Utah reported on the technical evaluation of breast magnetic resonance-guided FUS (MRgFUS) first-in-human clinical trial. The Breast MRgFUS System was devised to address the challenging imaging environment of breast tissue. Treatment lasted 73 to 114 minutes with no sedation. The treatment has been shown effective for 1- to 3-cm tumors. The 3-D MR-acoustic radiation force imaging can be repeated in the same tissue. 3-D MR temperature imaging was monitored for safety and efficacy. Studies showed that this can be done without sedation to ablate 1- to 3-cm tumors in less than 90 minutes.

Chrit Moonen from University Medical Center, Utrecht, reported on MR-HIFU in breast cancer clinical trials at Utrecht. Their treatment used a circular wide-aperture transducer that surrounds the breast. The phase 1 clinical trial showed that it is a safe system, and the phase 2 clinical trial was approved but interrupted by COVID-19. The primary endpoint is effectivity; the secondary is safety. A second phase 1 study is planned to assess the safety and tolerability of combining MR-HIFU hyperthermia and ThermoDoxR. MR-HIFU has a big role to play of the future.

David Brenin from the University of Virginia updated participants on the use of focused ultrasound at the university, particularly the use of focused ultrasound ablation (FUSA) for tumors in the breast. Step-wise trials were initiated for the treatment of benign fibroadenomas and for advanced breast cancer. The fibroadenomas exhibited a 69% reduction in volume, and the treatment was feasible and safe. The trials have enrolled 100 patients but must await the end of COVID restrictions to proceed. For metastatic or stage 4 breast cancer, FUS was combined with Pembrolizumab, which was given either before or after FUS. For the 10 women enrolled to date, side effects have been acceptable.

1 Questions to all

Clinical “staying power” is often related to patient throughput. What are the barriers to reducing the cost and duration of treatment?

Patients are concerned about the cosmetic results of surgery, about the time treatment takes, and about cost.

MRI or contrast-enhanced imaging does not work for treatment monitoring. We use diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC), whether they enhance or not. We need to combine all parameters of sequences to find a good response.

The clinician’s goal is controlled disease. But treating 100% of a tumor for success may be a false bar for success. We need a good biomarker of disease. We can always re-biopsy.

Whether using MRI or FUS guidance, there are many ways to monitor treatment. We need to assess treatment to see if it is working. With FUS, we are asking the patient to go with a nontraditional treatment.

.

Prostate Cancer

Special Lecture

Howard Soule, MD

Prostate Cancer Foundation



Howard Soule, MD

In this special lecture, Howard Soule, MD, described the work of the Prostate Cancer Foundation in discovering new treatments for advanced prostate cancer. Over the past 27 years, the Prostate Cancer Foundation (PCF) has raised more than \$830 million to fund 2,200 research projects at 220 institutions in 22 countries around the world. These studies helped to significantly lower the US mortality rate, created new funding models, recruited the best global scientists, and created new public-private collaborations. All recently approved pharmaceuticals for prostate cancer have been a part of PCF's portfolio. Because of the disproportionate number of deaths in males from the COVID-19 pandemic, PCF studied the relationship between the novel coronavirus and TMPRSS2, the most frequently altered gene in primary prostate cancer. The foundation held two global knowledge exchanges and then launched two clinical trials to create COVID-19 treatments.

PCF has made many historic achievements along the road to improving care for prostate cancer, including early involvement in creating precision medicine solutions. Studying metastatic biopsies allowed researchers to provide information that helped clinicians choose treatments based on the genomic characteristics of the tumor, a methodology that is now used throughout medical oncology worldwide. Two international "dream teams" recruited large cohorts of patients to provide biopsy tissue for genomic studies. Significant advances in molecular imaging and novel treatments have also been funded by PCF. Finally, an unprecedented program to deliver precision care to veterans has been achieved by funding nationwide centers of excellence. PCF has a dynamic young investigator program to fund and develop the next generation of leaders in the field. The three-year, \$150,000 grant covers research expenses, salary, and protected research time in a global community based on working groups.

.....

Prostate

Oral Presentation Q&A

Presentations highlighted novel ultrasound technologies and outcomes from studies of focal therapy in patients with localized prostate cancer.

MODERATOR

Samuel Peretsman | Urology Specialists of the Carolinas

SPEAKERS

Sandeep Arora | Vanderbilt University Medical Center

MRI-guided transurethral ultrasound ablation (TULSA) in men with localized prostate cancer: two-year follow-up

Yoni Hertzberg | NINA Medical

Real-time US imaging of HIFU field and applications to focal therapy of the prostate

Rahul Mehan | East Valley Urology Center

HIFU prostate ablation results in a single-center community practices

Thomas Payen | LabTau

Monitoring clinical HIFU lesion in prostate cancer using passive elastography based on conventional B-mode images

Deepika Reddy | Imperial Prostate

Oncological outcomes of 356 patients undergoing focal ablative salvage therapy (HIFU or cryotherapy) following radiation failure for prostate cancer

Cancer control outcomes following focal therapy using HIFU in 1,793 men with non-metastatic prostate cancer treated over 15 years

Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score matched study

George R. Schade | University of Washington

Transrectal boiling histotripsy of the prostate: initial pre-clinical results with a prototype device

Sunao Shoji | Tokai University School of Medicine

Focal therapy with high-intensity focused ultrasound for the localized prostate cancer for Asian patients: Prospective analysis of oncological and functional outcomes

1 Question to Dr. Arora

Outcomes in the trial of MRI-guided transurethral ultrasound ablation (TULSA) were influenced by the presence of intraprostatic calcifications. What were the trial's exclusion criteria for calcifications, and were specific guidelines available on the use of TULSA in the presence of calcifications?

The original trial inclusion criteria had allowed calcifications up to 1 cm. However, during the trial it became clear that calcifications smaller than 1 cm could be problematic. MRI thermometry does not work well in the presence of calcifications. Furthermore, different

MRI sequences need to be used to visualize calcifications. TULSA may be used if the calcification is not located in the center of the ultrasonic beam generator, such that the introducer can be directed above or below it. However, outcomes in this setting have not been systematically studied.

2 Question to Dr. Arora

Are patients who have previously been treated with transurethral resection of the prostate (TURP) candidates for TULSA?

There should be no impediment to the use of TULSA in patients who have undergone TURP. Some patients previously treated with TURP have subsequently received TULSA; however, as yet the number of such patients is too small to enable any conclusions to be drawn.

3 Question to Dr. Arora

Post-procedural pad usage was about 7.5% in the study. Was this a particular concern for apical tumors?

Lesions at the apex of the sphincter were treated very conservatively. Only one patient in the trial had to use more than one pad per day; the rest used a “safety pad.”

4 Question to Dr. Mehan

Could you briefly describe your urethral-sparing technique?

He preserves one lane of tissue, or about three degrees, on each side of the catheter. He removes the catheter to treat tissue around or above it, and then replaces it.

5 Question to Dr. Payen

Do you foresee being able to use passive elastography synchronously during thermal ablation?

Real-time use of the technology in the clinic is the goal, and his team is confident that this will soon be possible.

6 Question to Dr. Reddy

Is focal ablative salvage therapy following radiation failure deemed standard of care in the United Kingdom, and is the procedure well accepted clinically?

Currently the UK's National Institute for Health and Care Excellence allows the use of focal therapy using HIFU or cryotherapy provided that data are being collected either in clinical trials or prospective databases. Clinical acceptance is mixed, with some highly motivated patients seeking out this treatment option, while other patients are less accepting of a novel therapy. Reddy and her colleagues have initiated a clinical trial, CHRONOS, which is aimed at understanding the acceptability of focal compared with radical therapy.

7 Question to Dr. Reddy

In the United States, patients with persistent disease either in or out of field after HIFU typically move on to whole-gland therapy. In the UK, by contrast, persistent disease following HIFU is not considered treatment failure and patients may undergo a second HIFU procedure. What data does your group have on the efficacy of second treatments?

About 25% of patients had a Gleason score of 3 + 4 or higher after one primary HIFU

treatment, and about 18% underwent retreatment in any form. About 200 patients had an additional HIFU session and no further treatment, while around 80 to 90 patients opted for whole-gland therapy as a second treatment.

8 Question to Dr. Schade

Please share your thoughts on the advantages of histotripsy versus a technology that uses both mechanical and thermal effects.

The loss of scatter with mechanical ablation potentially provides a quantitative way to measure the efficacy of ablation.

9 Question to Dr. Hertzberg

When might real-time ultrasound (US) imaging of the HIFU field transition into clinical use?

A clinical trial of this technology is expected to begin in about 18 months.

.

Prostate

Panel

MODERATOR

Howard Soule, Prostate Cancer Foundation

PANELISTS

Clare Tempny | Brigham & Women's Hospital, Harvard Medical School

MR guided focused ultrasound for focal prostate cancer: Trial update, lessons learned and outcomes

Cary Robertson | Duke University

HIFU in localized prostate cancer

Stephen Scionti | Scionti Prostate Center

Transrectal (US guided) vs transurethral (MR Guided) approach: Compare and contrast

Mark Emberton | University College, London

Failure and rescue: Mechanisms and management of recurrence

Clare Tempny from Brigham and Women's Hospital, Harvard Medical School, reported that the first phase 2b multicenter study of MRgFUS focal therapy for intermediate-risk prostate cancer conducted in the United States (Ehdaie et al., presented at the 2020 American Urological Association) concluded that focal MR-guided FUS appears to be safe, feasible, and effective for Grade Group 2 disease at 6-month biopsy. At 6-month MR-targeted biopsy, 91% of men had no evidence of prostate cancer in the treatment area; 96% had no evidence of Grade Group >2 disease. Serum PSA measurements decreased after treatment and stabilized after 6 months. Biopsy data at 24 months are pending. Controversies remain regarding optimal patient selection, the use of heterogeneous methods and ablative techniques, appropriate measures of success, and optimal approaches to follow-up and imaging of

recurrence. An international consensus panel of the European Association of Urology has proposed standardized nomenclature and surveillance methodologies after focal therapy and partial-gland ablation for localized prostate cancer (Lebastchi et al., 2020). Among the panelists, 97% agreed that at present multiparametric MRI is the imaging modality of choice for evaluating treatment response; 81% agreed that early contrast enhancement in the treated lesion is suggestive of failure after focal therapy.

Cary Robertson from Duke University reported on lessons learned from prostate HIFU: Optimal HIFU energy delivery needs to be better understood. Biopsy positivity may not predict immediate failure for low- or intermediate-grade disease. Imaging may be informative without being definitive. Criteria for failure are evolving for all ablative therapies and may be subject to re-interpretation of long-term results based on patient outcome and not necessarily the presence or absence of residual disease. The incidence of HIFU treatment failure in high-grade disease is similar to that of other therapies, suggesting multifactor causation.

Stephen Scionti from Scionti Prostate Center reported that, in contrast with HIFU, TULSA offers real-time MRI planning and temperature monitoring as well as robotic closed-loop ablation control. At any time during treatment with TULSA, the treating physician can pause, adjust the treatment plan, and touch up any regions. TULSA may be particularly suitable for the treatment of larger prostates, especially in the presence of benign prostatic hyperplasia, and for the treatment of anterior lesions where HIFU may have limitations. As a new technology, TULSA is not currently reimbursable in the United States, whereas mechanisms are now in place for reimbursement of HIFU. Medicare reimbursement criteria have been defined and a CPT code will be available in January 2021.

Mark Emberton from University College, London, observed that, although failure is unfortunately associated with all cancer therapies, much can be done to mitigate both early (in field) and late (out of field) failure. Case selection and planning are probably the most important aspects of failure mitigation.

1 Question to all

Submitted by a prostate cancer survivor: Eight years after a radical prostatectomy, he has now experienced a biochemical recurrence and is wondering what he should do next.

Dr. Emberton: Salvage external-beam radiotherapy; it would be difficult to perform FUS without a target. Studies suggest that recurrence is likely to be located in the prostate bed. In the post-radical prostatectomy and post-radiation therapy setting, HIFU could be appropriate treatment for a recurrence that was visible on PET or MRI; however, patients would have to be carefully selected.

Dr. Tempany: The first step before making any treatment decisions should be to obtain a high-quality image. Multiple guidelines now support performing a pre-biopsy MRI to define focal lesions, volume, and margins.

2 Question to all

Should patients be treated with focal therapy such as HIFU outside of a clinical trial?

Dr. Scionti: Ideally, focal therapy should be performed under a defined protocol with rigorous selection criteria, standardized procedures, and reported results. Allowing focal therapy to be used outside of a trial setting could lead to lack of standardization and treatment of patients who are not good candidates for this treatment approach.

Dr. Tempny: Limiting the use of focal therapy to clinical trials has been the approach at her institution, Brigham and Women's Hospital.

Dr. Robertson: Duke University is participating in the Focal Robotic Ultrasound Ablation Registry, which is collecting outcome data on patients who have undergone HIFU focal therapy for prostate tissue ablation. This experience has led to a narrowing of the selection criteria for HIFU therapy.

Dr. Emberton: After 13 years of experience with focal therapy in multicenter and randomized settings, its safety profile and early-to-medium-term outcomes are well known, although data are limited on outcomes beyond 10 years. Optimal performance, careful follow-up, and collection of outcome data are provider responsibilities in all settings. Trials are needed in areas where uncertainty remains, such as whether to use adjuvants. However, limiting all use of focal therapy to clinical trials poses issues of both practicality and equitable access to treatment.

3 Question to Dr. Tempny

Please discuss the challenges of MRI for prostate cancer and its potential for variability in the community setting.

A 2016 survey found that 72% of urologists in academic settings were using MRI for prostate cancer, while 38% of urologists in private practice were doing so. MRI is very expensive and access to it is a global problem. Inter-reader variability will never be eliminated. It has been recommended that radiologists read at least 100 cases to attain an expert proficiency level.

4 Question to Drs. Scionti and Robertson

Please comment on the patient characteristics that predict the greatest benefit from focal therapy.

Dr. Scionti: Patients most interested in focal therapy are those who prioritize preservation of function. In general, disease burden and tumor location determine which structures can be preserved. A candid discussion between the patient and physician about the patient's preferences and risk for recurrence, particularly out-of-field recurrence, is an important part of shared decision-making.

Dr. Robertson: The ideal patient is the one who will have the best result from treatment. Patient characteristics should include low- to intermediate-Grade Group 2 organ-confined disease and a small, readily targeted prostate in a good location, usually posterio-lateral.

5 Question to all

How do you deal with cancer that cannot be seen, and how does this affect the outcomes of focal therapy?

Dr. Emberton: An odd question because—at least in solid tumors—the presence of cancer is defined by imaging. With the exception of the hematologic cancers, oncology lacks a means of measuring or monitoring cancer that cannot be visualized.

Dr. Robertson: The prostate is the only organ that is systematically biopsied to diagnose a malignancy; every other cancer is diagnosed on the basis of an image or physical finding. In Gleason 6 disease, 60% may not be visible, but may also not be significant. In organs other than the prostate, indolent tumors are often treated conservatively.

6 Question to Dr. Emberton

Please discuss the status of sonodynamic technology for ablating the prostate.

Sonodynamic therapy involves the initiation of nanoparticles by exposure to sound energy. A patient receives an injection of nanoparticles, which find their way to a cancer somewhere in the patient's body. A week later, the nanoparticles are activated by waving a diagnostic-specific US device across the organ of interest. The sound waves release oxygen free radicals that have an immediate, short-term killing effect. The technology is noninvasive, causes few if any significant side effects, and can be performed by health care workers with relatively little training, making it a particularly attractive option in low-resource environments.

Dr. Emberton's laboratory is currently conducting preclinical studies of sonodynamic therapy. To date, reliable necrosis has been achieved in most animals and most tumors. The team plans to conduct confirmatory preclinical studies before moving to a first-in-humans study in men prior to cystectomy or radical prostatectomy. The first-in-humans study could begin in about two years.

7 Question to all

Where do you see focal therapy going in the future?

Dr. Tempny: The future will be in imaging and, in particular, in the specificity of the targets used.

[The session time ran out before other panelists could answer.]

• • • • •

2020 Awards Ceremony

2020 Visionary Award



Lawrence A. Crum, PhD

A leading expert in the fields of focused ultrasound and acoustics, **Lawrence A. Crum**, PhD, has been selected for the Focused Ultrasound Foundation's 2020 Visionary Award. This 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. During this year's virtual meeting format, Dr. Crum will give a presentation on the path focused ultrasound has undergone from the Fry brothers to today and his vision for the technology's future.

Dr. Crum recently retired after a 25-year career in the field. Most recently he was Research Professor of Bioengineering and Electrical Engineering at the University of Washington (UW), Principal Physicist in UW's Applied Physics Laboratory, and founder/past director of the Center for Industrial and Medical Ultrasound.

"Larry is one of the few true pioneers in the field of focused ultrasound," said FUSF Chairman Neal F. Kassell, MD. "From the beginning, he understood the technology's immense potential to help countless patients and led the field in both research and commercialization. We can all benefit from his insight on the opportunities that lie ahead."

A self-proclaimed "bubble expert," Dr. Crum received his doctoral degree in physics from Ohio University and became interested in cavitation during his postdoctoral work at Harvard University. This interest collided with the field of focused ultrasound in 1994, when he was asked to consult on a new treatment for benign prostatic hyperplasia. That relationship led Dr. Crum to help establish the company that is now SonaCare Medical. Over the years, he co-founded three additional companies—Therus, Ekos, and Ultrasound Technologies—and the International Society for Therapeutic Ultrasound (ISTU).

He has held positions at Harvard University, the US Naval Academy, and the University of Mississippi, where he was F.A.P. Barnard Distinguished Professor of Physics and Director of the National Cancer Center for Physical Acoustics.

Dr. Crum has published more than 220 articles in professional journals (with a Google Scholar h-index of 84) and has been awarded 21 patents. He was recently awarded the Gold Medal of the Acoustical Society of America, its highest honor.

"The ultimate goal of most medical researchers is to participate in the development of a new technology that has a major impact on the health of our general society," said Dr. Crum. "I am confident that focused ultrasound will be one of those technologies."

Previous Visionary Award recipients have included Narendra Sanghvi, PhD (2018), Kullervo Hynynen, PhD (2016), and Motti Zisser (2014).

Dr. Crum's Visionary Award lecture, titled "Perspectives on the future of therapeutic ultrasound," highlighted the work of six of his colleagues who are building the future of the

technology. He encouraged young investigators to attend professional meetings, volunteer to assist with organizing meetings, make friends with other researchers, and learn to collaborate rather than compete.

.....

2020 Ferenc Jolesz Memorial Award

Now in its third year, the Ferenc Jolesz Memorial Award has a two-fold purpose: to honor the memory of Ferenc Jolesz, a world-class visionary with a passion for pushing surgery into the 21st century and a pioneer of focused ultrasound as a noninvasive therapy, and to recognize and encourage this same innovative spirit in midcareer researchers and clinicians who continue to advance focused ultrasound.



Nir Lipsman, MD, PhD, FRCSC

We are honored to present the award to **Nir Lipsman**, MD, PhD, FRCSC, a neurosurgeon and scientist at Sunnybrook Health Sciences Centre and Sunnybrook Research Institute. Dr. Lipsman is currently the director of Sunnybrook's Harquail Centre for Neuromodulation, and the clinical director of Sunnybrook's Focused Ultrasound Centre of Excellence. He also serves as an assistant professor in the Department of Surgery at the University of Toronto.

Over the last 10 years, Dr. Lipsman has pioneered several clinical applications of MR-guided focused ultrasound in novel indications, including essential tremor, Parkinson's disease, obsessive-compulsive disorder, and major depression. He has also initiated critical research investigating focused ultrasound's ability to temporarily open the blood-brain barrier in patients with a variety of debilitating diseases, including Alzheimer's disease, ALS, and primary and secondary brain tumors.

"It's an incredible honor to receive this award in Dr. Jolesz's name, a giant and pioneer in the focused ultrasound field," said Dr. Lipsman. "I share it with the amazing team at Sunnybrook and all our collaborators, without whom none of this exciting work would be possible."

Dr. Lipsman received his undergraduate degree from the University of Toronto. He went on to earn his medical degree from Queen's University and completed a neurosurgical residency and PhD at the University of Toronto.

The Ferenc Jolesz Memorial Award is supported by Insightec and presented at the foundation's biennial symposium. It includes a \$5,000 cash prize. Previous Jolesz Award recipients have included Seung-Schik Yoo, PhD, MBA (2018) and Nathan McDannold, PhD (2016).

Dr. Lipsman's Jolesz Award lecture, titled "Standing on the shoulders of giants: Disrupting neurosurgery with focused ultrasound," described how disruption in medicine produces transformational change that influences how a diagnosis is determined and how diseases are treated. Focused ultrasound began disrupting the field of neurosurgery in 2006 and has rapidly evolved to the point where Sunnybrook Health Sciences Centre has investigated its use across virtually every discipline of neuroscience: neurodegenerative disorders, movement disorders, blood-brain barrier opening, cancer, and psychiatry.

.....

2020 Andrew J. Lockhart Memorial Prize

Matthew Bucknor, MD, associate professor of radiology at the University of California, San Francisco (UCSF), and **Pejman Ghanouni**, MD, PhD, assistant professor of radiology at Stanford University, were awarded the 2020 Andrew J. Lockhart Memorial Prize.



Matthew Bucknor, MD

The \$75,000 prize is awarded annually to investigators in recognition of their outstanding contributions in advancing cancer treatment using focused ultrasound and their potential for continued achievements in the field. The prize was established in 2017 by the family and friends of Andrew J. Lockhart, who passed away in 2016 at the age of 39 after a hard-fought battle with cholangiocarcinoma, an aggressive, malignant cancer affecting the biliary system.

In a break from tradition, the foundation chose to award two prizes this year. “Dr. Bucknor and Dr. Ghanouni’s active collaboration and passion for the treatment of intractable cancers—coupled with their particular interest in immune-based focused ultrasound treatments—made these two applicants equally deserving of the award,” said Jessica Foley, PhD, the foundation’s chief scientific officer.

Matthew Bucknor

Dr. Bucknor has made significant contributions in the field of focused ultrasound cancer therapy and concentrates his research on work that will directly impact the care of cancer patients in the near term. The results of his studies have been incorporated into treatment protocols internationally, helping to improve outcomes for patients with benign and malignant tumors of bone and soft tissue. He has also collaborated with other investigators in efforts to combine focused ultrasound with novel immunotherapies to improve patient outcomes.

Serving as the director of Focused Ultrasound at UCSF since 2014, Dr. Bucknor has pioneered treatments for desmoid tumors, bone metastases, and osteoid osteomas. He has treated more than 60 patients, which combined with his prior work at Stanford in collaboration with fellow prize recipient Dr. Ghanouni, makes him one of the most experienced physicians in the country treating musculoskeletal diseases using focused ultrasound.

Dr. Bucknor also has a passion for mentorship and fostering development of the next generation of focused ultrasound researchers. In recognition of his work as chair of his department’s Diversity and Inclusion committee, he was awarded the Chancellor Award for Dr. Martin Luther King Jr. Leadership in 2019, UCSF’s highest honor for diversity-related service work.

“I have been fortunate to have the opportunity to make significant contributions to the improvement of cancer treatment through my research and clinical activities in focused ultrasound,” said Dr. Bucknor. “I am excited to contribute to the next great discoveries in the field.”

Pejman Ghanouni

Dr. Ghanouni has focused his work on developing techniques that could lead to more effective therapeutic interventions for hard-to-treat diseases. He established and leads Stanford’s Minimally Invasive MR Interventional Center and co-directs Stanford’s Focused Ultrasound Center of Excellence. Working as part of a multidisciplinary team, he has led



Pejman Ghanouni, MD, PhD

several clinical trials of focused ultrasound at Stanford that contributed significantly to FDA approval of the technology to treat patients with painful bone metastases, debilitating essential tremor, and symptomatic uterine fibroids; co-led trials at Stanford to treat prostate cancer and Parkinson's disease; and pioneered the application of MR-guided focused ultrasound for treatment of soft tissue tumors, such as desmoid tumors.

Aside from his clinical work, Dr. Ghanouni is a champion for improving focused ultrasound's efficacy and safety and has engaged in multiple collaborative technical projects that have advanced the field.

"I am proud of what I have been able to achieve so far for our patients and others like them, and I am very excited by the opportunity to lead the development of future applications of this technology," said Dr. Ghanouni.

Drs. Bucknor and Ghanouni presented their award-winning work in a November 5, 2020, webinar.

.....

Young Investigator Award Recipients

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

Graduate students, research fellows, clinical fellows, and junior faculty members are eligible to apply for the awards, which—due to the transition to a virtual meeting in 2020—includes a \$1,000 cash prize. This year, we recognized nine individuals from four countries, and for the second time, Bracco Suisse SA elected to sponsor a Young Investigator Award recipient. This year they selected Avinash Eranki, an assistant professor and principal investigator of the Medical Ultrasound Research laboratory at the Indian Institute of Technology. Eranki presented his research, titled "Immune sensitization and therapeutic impact of boiling histotripsy in refractory murine neuroblastoma."



Abdul-Kareem Ahmed, MD

Awarded for: Bilateral magnetic resonance-guided focused ultrasound thalamotomy of the central lateral nucleus for medically refractory neuropathic pain [CHP-001]

Abdul-Kareem Ahmed is a third-year neurosurgery resident at the University of Maryland. He studied neuroscience and philosophy at the University of Pittsburgh and earned his master's in science writing at MIT. He completed medical school at Brown University, where he was awarded the American Association of Neurological Surgeons (AANS) Medical Student Research Fellowship. He was also awarded the American Brain Tumor Association (ABTA) Medical Student Research Fellowship for studying immune checkpoint blockade for glioblastoma. At the University of Maryland, Dr. Ahmed is invested in focused ultrasound, studying methods to improve eligibility and outcomes in movement disorder patients with Dr. Howard Eisenberg, assisting in a trial to open the blood-brain barrier in glioma patients with Dr. Graeme Woodworth,

and working on a trial for treating neuropathic pain with Dr. Dheeraj Gandhi. Dr. Ahmed hopes to one day bring focused ultrasound technology to his home state of Rhode Island.



Harshini Ashar

Awarded for: Immunological and therapeutic effects of focused ultrasound in canine cancer patients [IMM-001]

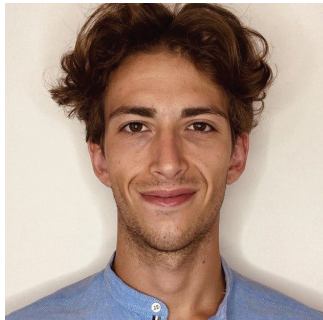
Harshini K. Ashar is a PhD candidate under the mentorship of Dr. Ashish Ranjan in the Nanomedicine and Targeted Therapy Laboratory at Oklahoma State University. Her research is investigating the effects of focused ultrasound and nanoparticles on chemo-immunotherapy of chronic musculoskeletal infections and spontaneous canine cancers. She earned her bachelor and master of veterinary science (BVSc and MVSc) degrees from Maharashtra Animal & Fishery Sciences University in Maharashtra, India.



Benjamin Davidson, MD

Awarded for: Magnetic resonance-guided focused ultrasound capsulotomy for psychiatric disorders: Clinical results and neuroimaging analysis [PSY-001]

Benjamin Davidson is a fourth-year neurosurgery resident at the University of Toronto. He is in his final year of graduate studies, completing a PhD under the supervision of Dr. Nir Lipsman and Dr. Clement Hamani. He is developing novel neurosurgical treatments for treatment-resistant psychiatric disorders and using neuroimaging tools to help predict and explain responses to psychiatric surgery.



Alessandro De Maio

Awarded for: MR-guided focused ultrasound versus external radiation therapy for the treatment of pain in bone metastases, a multicenter open-label phase-two clinical trial [MSK-003]

Alessandro De Maio is in his final year of medical school and is active in diagnostic and interventional imaging at La Sapienza University of Rome. He has been working with Dr. Alessandro Napoli and his team since 2017, where he had the opportunity to learn more about focused ultrasound technologies and become involved in bone metastases clinical trials. His selected honors include a Sapienza Excellence scholarship and research program fellowships with the University of Lund and University of Uppsala, where he worked with experts in the field of neuroimaging and MRI physics. He plans to pursue a career in science and radiology and expresses enthusiasm for focused ultrasound therapies and emerging applications.



Avinash Eranki, PhD

Awarded for: Immune sensitization and therapeutic impact of boiling histotripsy in refractory murine neuroblastoma [IMM-006]

Avinash Eranki is an assistant professor and principal investigator at the Medical Ultrasound Research laboratory within the Department of Biomedical Engineering at the Indian Institute of Technology in Hyderabad, India. He has been working on therapeutic ultrasound for more than six years and on medical ultrasound for over a decade. He worked with Prof. Chrit T.W.

Moonen and Dr. Mario Riesat at University Medical Center in Utrecht, Netherlands, where he received his PhD. He also worked with Dr. Bradford J. Wood at the National Institutes of Health Clinical Center and the IGNITE group at Children's National Hospital on developing novel therapeutic ultrasound techniques for solid tumor therapy in combination with immunotherapy and chemotherapy. Dr. Eranki is currently on the editorial board of the journal *Ultrasound in Medicine and Biology* and serves as a reviewer for several other ultrasound and imaging journals.



Kisoo Kim, PhD

Awarded for: Sonication strategies for delivery of volumetric ultrasound hyperthermia using the ExAblate body array [TEC-008]

Kisoo Kim received his BS and MS degrees in biomedical engineering at Kyung Hee University in Seoul, Korea, and earned his PhD at Strasbourg University in France in 2019. His dissertation work involved the development of quantitative MRI techniques (simultaneous MR elastography and MR thermometry) for the evaluation of MR-guided ultrasound thermal therapy. He currently works as a postdoctoral scholar under the mentorship of Drs. Chris Diederich and Eugene Ozhinsky at the University of California, San Francisco, to develop motion-robust, multislice, real-time MR thermometry for MR-guided ultrasound thermal therapy in abdominal organs (e.g., pancreas, liver, and kidney). Additionally, Dr. Kim is developing a beamforming strategy for volumetric hyperthermia using the Exablate body system. He pursues a long-term research interest in developing relevant MR/ultrasound techniques for MR-guided ultrasound thermal therapy and achieving great growth in the field.



Mehmet Ozdas, PhD

Awarded for: Non-invasive receptor-specific millimeter-precision manipulation of brain circuits by ultrasound-mediated aggregation and uncaging of drug carriers: in-vivo results [NMD-007]

Mehmet S. Ozdas received his MSc in Analogue and Digital Integrated Circuit Design from Imperial College London and his PhD from the Swiss Federal Institute of Technology Zurich (ETH Zurich) in 2019. During his PhD dissertation research at the Neurotechnology Laboratory of Prof. Mehmet Fatih Yanik, he worked on focused ultrasound and ultrasound-sensitive drug carriers to remotely concentrate drugs in the brain with millimeter resolution and orders of magnitude higher efficiency than systemic drug delivery. Dr. Ozdas and colleagues demonstrated that blood-brain barrier (BBB) penetrating drugs can be focally delivered to specific brain regions without the need for BBB disruption via a novel focused ultrasound sequence, ultrasound-sensitive drug carriers, and in-vivo electrophysiology. He is currently a postdoctoral fellow in the Diffuse Midline Glioma Research Center of the University Children's Hospital Zurich and the Neurotechnology Laboratory of ETH Zurich, where he is developing novel tools for therapeutic interventions specifically for CNS disorders, including intractable childhood brain tumors. His research employs focused ultrasound, in vivo electrophysiology, ultrasound-sensitive drug carriers, and in vivo microdialysis.



Mohit Pratap Singh, PhD

Awarded for: Boiling histotripsy and CD40 activation re-sensitize the immunologically “cold” tumor to checkpoint blockade therapy [IMM-017]

Mohit Pratap Singh, PhD, received his Bachelor of Veterinary Science degree (DVM equivalent) from Madras Veterinary College, India, and MS in Veterinary Surgery from G B Pant University of Agriculture and Technology in Pantnagar, India. He began work on his PhD in the College of Veterinary Medicine at the Oklahoma State University in 2015, where he worked in Dr. Ashish Ranjan’s laboratory. Dr. Singh explored the role of combining focused ultrasound therapy with gene-delivering nanoparticles and anti-CD40 agonistic antibodies in improving the tumor microenvironment in a poorly immunogenic model of melanoma. His interest lies in exploring novel ways of applying focused ultrasound therapy with various immune modulators, such as nanomedicine and biologics, and shaping a patient’s immune system to fight cancer.



Kristiana Xhima, PhD

Awarded for: Delivery of a selective TrkA agonist to the brain using transcranial focused ultrasound enhances cholinergic function and rescues cognition in a mouse model of Alzheimer’s disease [NDG-008]

Kristiana Xhima is a postdoctoral fellow in Dr. Isabelle Aubert’s lab at Sunnybrook Research Institute. She recently completed her PhD in the Department of Laboratory Medicine and Pathobiology and Collaborative Program in Neuroscience at the University of Toronto. Her research centers on focused ultrasound applications for neurodegenerative diseases, including ultrasound-mediated delivery of neurotrophic factors and gene therapies. She graduated from the University of Toronto with a BSc in pathobiology and neuroscience (with honors) in 2015.

.....

Pancreatic Cancer

Oral Presentation Q&A

Presentations described phase 1 to phase 3 studies in treatment modalities for pancreatic cancer.

MODERATOR

Joan Vidal-Jové | Institute Khuab for Interventional Oncology

SPEAKERS

Michael Gray | University of Oxford

Planning and delivery of ultrasound-mediated hyperthermia for clinical targeted drug delivery

Alissa Hendricks | Virginia Polytechnic Institute and State University

Histotripsy is an effective pancreatic tumor ablation strategy that releases immunostimulatory molecules and promotes anti-tumor immunity

Jordan Joiner | The University of North Carolina at Chapel Hill

Low-intensity focused ultrasound produces immune response in pancreatic tumors

Tatiana Khokhlova | University of Washington

Chronic effects of cavitation-aided gemcitabine delivery to pancreas cancer on tumor microenvironment in KPC mouse model

Petros Mouratidis | Institute of Cancer Research, London

Demonstration of the use of microbubbles combined with low pressure pHIFU to induce cavitation and anti-cancer effects in pancreatic tumor

Eleanor Stride | University of Oxford

Sonodynamic therapy for pancreatic cancer

1 Questions to Dr. Gray

Why use Thermodox?

Thermodox has been successfully used in liver cancer. High-frequency jet ventilation from a centimeter to a few millimeters was used for ventilation and to speed the process.

Your heating model now includes organ motion. Could you elaborate on that? How does it deal with aperiodic motion, e.g., bowel motion?

This was seen in only one patient. We used trimoxazole to see the difference with and without high-jet ventilation. The US-guided technique minimized variability of the procedure.

2 Question to Dr. Hendricks

Have you tried inflammatory markers?

We have not looked at changes in cytokine profile. The study has an in vitro and an in vivo arm to look at full ablation and its effect on the tumors.

3 Questions to Dr. Joiner

One difference with pancreatic tumors is the physical barrier outside the tumor.

Can mechanical means be used to cross the tumor barrier?

Microbubbles seem effective and we hope microcavitation will allow microbubbles to facilitate drug delivery. Further studies are needed to refine ultrasound and microbubble treatment timing in order to optimize approaches, combine this with immunotherapy, and move this technology toward clinical translation.

How do you foresee continuation of this research?

We want to study the effect of tumor size on the cells that are coming inside. It is definitely a time-related course. Often diagnosis occurs late in the disease. We want to repeat with an orthotopic model to use tail-vein infusion and then back-calculate the full rate of microbubbles to the tumor.

4 Question to Dr. Khokhlova

Your research shows that timing is important.

After immunosuppression, the tumor remained. We treated weekly to disrupt the tumor, but the endpoints may have been calculated too soon. Results showed that the cells were dying, so maybe the immune system did not have enough time. A group of mice received nothing, another groups received gemcitabine, and a third received a combination. We used genetically engineered ABC mice, so tumors could be occurring in other places. Tumors will metastasize, usually to liver and lungs, but endpoints were too restrictive to see that.

5 Question to Dr. Mouratidis

With microbubble infusion, rather than injection, sometimes huge benefit is more worrisome. What about tissue damage done?

Damage in the blood vessels was not that great. It is difficult to be sure whether the damage is real or is a necrotic part of the tumor that would be there anyway. This can be seen more clearly if the pressure is increased.

.

Pancreatic Cancer

Panel

MODERATOR

Joo-Ha Hwang | Stanford University

PANELISTS

Holger Gröll | University of Cologne

Towards pancreatic cancer ablation using magnetic resonance-guided high intensity focused ultrasound (MR-HIFU): A preclinical safety and feasibility study

Jae Young Lee | Seoul National University Hospital

Combined treatment of Gem/nPac and FUS for unresectable pancreatic cancer: Safety and initial efficacy

Srikanth Reddy | Oxford University

HIFU in pancreatic cancer: Preliminary experience of setting up a clinical trial in a western centre

Joan Vidal-Jové | Institute Khwab for Interventional Oncology

Gail ter Haar | Institute of Cancer Research, London

Holger Gröll from the University of Cologne discussed a preclinical safety and feasibility study on pigs that treats pancreatic cancer ablation using magnetic resonance-guided high-intensity FUS (MR-HIFU). The challenges to treatment are depth (the pancreas is located behind bowel and stomach tissue), presence of heat-sensitive structures, and complex motion patterns of the pancreas. They are now ready to go to a clinical trial.

Jae Young Lee from Seoul National University Hospital presented a safety and initial efficacy study of using combined treatment of gemcitabine and FUS for unresectable pancreatic cancer. They wanted to determine the optimal FUS intensity. The low- and high-intensity groups died, but the intermediate-intensity group survived. They will design a prospective randomized controlled trial.

Srikanth Reddy from Oxford University reported results of a clinical trial of HIFU to combat pancreatic cancer. The goal was to harness the immune system of the patient via HIFU and immune therapy.

Joan Vidal-Jové from the Institute Khwab for Interventional Oncology, discussed several years' experience of treating pancreatic cancer with FUS, the particular challenges, and what to avoid.

Gail ter Haar, Institute of Cancer Research, London

1 Questions to Dr. Gröll

What are the main barriers to getting this to clinical work?

Only Thermobox is available now. Pancreatic cancer is not that sensitive to doxorubicin, so a high dose may be necessary. It would also need temperature-sensitive liposomes. It could be good on a stable target, but we need something that works on moving targets. We need a clinical partner to bring this to the public and commercialization to get it into the clinic.

How long do you maintain the temperature?

The longer you treat, the more challenging.

What are the downsides to temperature-sensitive liposomes?

Doxorubicin can be delivered over 30 minutes. We see no downsides to that approach. When opening the blood–brain barrier, the circulation time of microbubbles is short but the permeability effect lasts much longer. It is more effective than drug-loaded bubbles themselves. Pharmacokinetics is not bound to the bubble but to the drug.

2 Questions to Dr. Lee

What is the difference between the intermediate, high, and low groups?

The high-intensity group had been treated previously, whereas the intermediate group had not. The conclusion is that the intermediate-intensity group had the best results.

What are the challenges of administering the drug (gemcitabine) and FUS closely together?

No issue at all. His department and the oncology department collaborated so they could coordinate the timing.

3 Question to Dr. Reddy

What challenges did you face in setting up the center?

They are competing for the same patients as other trials. The future lies in combining HIKU (completely noninvasive) with drug delivery. An important parameter to study is whether signals can be detected, and that the pool for the study must be expanded. Getting complete ablation with HIKU is unrealistic. We want a systemic response as well as immune modulators.

4 Question to Dr. Vidal-Jové

What do the clinical data with FUS show that should be avoided?

Pancreatic cancer is the most challenging gastrointestinal malignancy. Ablation with ultrasound is most effective. It is not invasive, repeatable, and you can see what you're doing.

To prevent small bowel or colon interference, we avoid bowel with positioning and water balloon use. To prevent tumor invasion of the duodenum, we do not treat the duodenum because of the risk of perforation or delayed fistula formation. A biliary stent can be placed. Bowel, biliary, or pancreatic duct obstruction post-treatment may cause cancerous cells to invade nearby vessels. The biggest challenge is bleeding from an artery. Another problem was fistula formation.

5 Question to Dr. ter Haar

More and more people are coming to the field, but they may not understand the complexities. How did practitioners get involved?

She is a physicist working in a hospital. She found the people in the hospital who were working on FUS. You need to know what you can and cannot target; which parts of the body reflect sound or absorb sound; whether bubble-based or heat-based treatment would be better. FUS is a difficult treatment to do, and you need to understand the principles involved in ultrasound. What we are missing is a basic textbook and training. Radiologists have a basis to build on.

• • • • •

Liver

Oral Presentation Q&A

Presentations described three treatments for liver tumors.

MODERATOR

Joan Vidal-Jové | Institute Khuab for Interventional Oncology

SPEAKERS

David Melodelima | LabTAU

Phase 1-2 study of intra-operative high intensity focused ultrasound in 35 patients with colorectal liver metastases

Sukumar Uday Kumar | Imperial College, London

Acoustically driven microbubbles enable targeted delivery of microRNA-loaded nanoparticles to spontaneous hepatocellular neoplasia in canines

Pete Weber | Virginia Polytechnic Institute and State University Carilion School of Medicine
Histotripsy for treatment of intrahepatic cholangiocarcinoma: feasibility study in excised human tumors

1 Question to Dr. Weber

What about treatment of tissues around the tumor? What is the safe range to avoid tissue damage, i.e., the mechanical index?

Increasing the number of pulses for dose/effect increases the image. The next step will be complete ablation of the tumor. More than 4,000 pulses causes a lot of damage. This group used a 700-kHz transducer, much stronger than the standard diagnostic probe.

.

Miscellaneous Tumors

Oral Presentation Q&A

Discussion centered on new techniques to treat subcutaneous tumors as well as tumors of the lung, head and neck, and colon.

MODERATORS

Karun Sharma | Children's National Health System

Jaime Murphy | Imperial College London

SPEAKERS

Jennifer Carroll | Virginia Polytechnic Institute and State University

HIFU for the treatment of subcutaneous solid tumors in canines

Petros Mouratidis | Institute of Cancer Research, London

Heat sensitizes colon cancer cells to HSP90 inhibition-induced cell death

Samuel Pichardo | University of Calgary

First experience in the treatment of recurrent, localized, and unresectable head and neck tumor using MRlgFUS-based hyperthermia

Frank Wolfram | SRH Wald-Clinic

Towards lung FUS: Jet ventilation during one lung flooding optimizes target motion and oxygenation independent of positioning

1 Questions to Dr. Carroll

Did you find skin burns related to depth of tumor? Was there a difference in ablation effect that corresponded with canine survival or with tumor types?

We did not see skin burns related to tumor depth, but we treat the animals a minimum of a half centimeter away from the skin. Neither did we see variation among tumor types. Survival times were typical for the type of tumor, and seemed not related to treatment. However, we treated and resected 6 days per week, so they probably would not have seen anything like that in this period.

2 Question to Dr. Mouratidis

Why did you choose this inhibitor, which is related to vascular development?

HSP90 is multifunctional. It is one hallmark of immunogenic cell death, it signals to macrophages, is involved in apoptosis, etc. We looked at hallmarks of immunogenic cell death and saw good relationships with HSP70 and HSP90. The effects changed in a time-dependent manner and did not exist after 3 or 4 days. The treatment had no effect on MCF7 breast cancer cells, but was seen in BT474 cells. The MCF7 cell line must not rely heavily on such proteins for survival. Heating them denatured them so HSP90 could help them survive. The inhibitor facilitates cell death. Cancer cells rely on overexpression, so HSP90 can be used to differentiate between cancer cells. This is about the overexpression of HSP90 in cancer cells.

3 Questions to Dr. Pichardo

How did you decide when to perform hyperthermia relative to radiotherapy—treat one week and give the next treatment one week later? Thermometry data show a wide variance; was this due to respiration or motion compensation? Was the twitching seen due to nerve stimulation or to the patient's surprise? Was unwanted heating observed near the bone?

This was mostly determined by the logistics of access to the equipment between departments. We only access once per week.

Movement was caused by breathing because we work so close to the diaphragm. Thermometry of patients with a higher tumor does not show that effect.

The twitching was caused by the patient's surprise and was improved by patient education. COVID-19 prevented them from treating more patients.

Heating was not observed near the bone.

4 Questions to Dr. Wolfram

Compare the results of pressure-controlled vs. jet ventilation. After the lung flooding procedure, do you remove the saline at the end of the procedure? How close to translation to humans is this practice?

We showed that jet ventilation reduces motion drastically compared with pressure-controlled ventilation. Otherwise, the two are approximately equal.

We also measured motion inside the lung. Motion from inside a flooded lung was very much reduced. We looked for specific targets that could be easily located.

Part (a maximum of 50%) of the fluid is drained; then the lung is reventilated. The rest of the liquid is resorbed by body perfusion within 30 to 40 minutes.

This procedure is not ready to be used on humans. This study shows the required technological steps in these techniques. The technological part is the missing part.

.

Thursday,
November 12, 2020



Clifton Leaf

Keynote Speaker

Clifton Leaf

FORTUNE

Mr. Leaf is editor-in-chief of FORTUNE magazine and the author of *Truth in Small Doses: Why We're Losing the War on Cancer—and How to Win It*. When attending symposia where scientists gather to share a vision and turn the improbable into the achievable, Mr. Leaf recalls President John F. Kennedy's 1962 speech, "We choose to go to the moon... and do the other things, not because they are easy, but because they are hard...that goal will serve to organize and measure the best of our energies and skills." While providing the example of building the crawlerway (the pathway at the Kennedy Space Center from the Vehicle Assembly Building to the launch pads) for the original moonshot in 1969, Mr. Leaf challenged the field of focused ultrasound to build the pathways and connected networks that provide common bioinformatics, communication tools, and access to shared data. He emphasized that technological platforms must be standardized and have the ability to communicate with one another (i.e., have interoperability) so that information can be quickly and easily shared to speed the rate of discovery. Agreement over a complex network run by standardized tools and rules is also what led to the creation of the Internet and what allows safe global air travel. Agreement on common frameworks, terminology, standards, and processes could prevent many problems in medicine, such as siloed electronic health records, clinical trial enrollment failures, and a lack of avenues for young scientists to conduct independent research. Similar to NASA's disastrous Ranger Program, curing cancer or Alzheimer's disease will not occur until prioritized clinical trials are truly interconnected with the patients and physicians who need them. Effective system management strategies are needed to do this.

.....

Blood–Brain Barrier Opening

Oral Presentation Q&A

Presentations highlighted preclinical studies investigating the use of different modalities of focused ultrasound (FUS), including holographic lenses and diffusor tensor imaging (DTI), blood–brain barrier (BBB) opening for the treatment of ischemic stroke, characterizing the inflammatory response following BBB opening, the treatment of brain metastasis, and viral vectors for drug delivery following BBB opening.

MODERATORS

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

Richard Price, University of Virginia

SPEAKERS

Sergio Jimenez Gambin | Universitat Politècnica de València

Bilateral blood-brain barrier opening in mice using acoustic holograms

Maria Eleni Karakatsani | Columbia University

Contrast-free detection of focused ultrasound-induced blood-brain barrier opening using diffusion tensor imaging

Antonis Pouliopoulos | Columbia University

A neuronavigation-guided clinical ultrasound system for blood-brain barrier opening at the bedside with real-time cavitation monitoring—Preclinical evaluation in non-human primates with behavioral amelioration and immunogenicity

Francesco Prada | Fondazione IRCCS Istituto Neurologico

Quantitative analysis of in-vivo microbubble distribution in the human brain: Impact on imaging and treatment

1 Questions to Mr. Jimenez Gambin

What is the reproducibility of the holographic lens between animals? How many multifocal spots could be made? Could the lens position be changed during the FUS procedure?

Reproducibility between animals depended on skull thickness. The number of multifocal spots depends on the wavelength of FUS; in this experiment the lens was designed to create two foci, but a lens could be designed to create up to five foci. The lens was capable of being moved to change the focus, but ideally the lens would be designed to treat that exact location in the skull.

2 Question to Dr. Jimenez Gambin

The microbubble dose was 1 μ L/g of bodyweight, which seems like a high dose.

Dr. Jimenez Gambin's collaborators at Columbia University had previously used the same microbubble dose, so the dose was used to maintain consistency across experiments.

3 Question to Dr. Karakatsani:

Would this technique work equally well in white and gray matter?

Prior research showed increased vascularity in gray matter, which makes it easier to open the BBB in gray matter. However, they noted changes in white matter as well as gray matter in these experiments.

4 Question to Dr. Karakatsani:

Can you compare DTI with a standard dynamic contrast enhanced (DCE) sequence for BBB opening, and were there any differences in sensitivity or other comparisons?

DCE uses a contrast agent and it took around one hour to acquire images, but DTI takes only 10 minutes. DTI is more sensitive than DCE. The goal is to avoid the use of gadolinium or any other contrast agents.

5 Question to Dr. Pouliopoulos

Regarding the observed improved cognition after BBB opening, what were the potential mechanisms?

Exact mechanisms are unknown. They hypothesize that functional connectivity could result in neurogenesis and other downstream effects. It is likely a function of the brain attempting to return to homeostasis. He also mentioned that there was a training effect, although the primates had previously trained on this task prior to this experiment.

6 Question to Dr. Pouliopoulos

Please describe the sonication with the human skull.

This was to test for cavitation parameters. They have been able to observe cavitation in humans as well. Currently, the aim is to avoid harmful effects of broadband emissions.

7 Question to Dr. Prada

Would the microbubble imaging method correlate to cavitation dose during BBB opening?

This was true. There are two factors that should be considered: the amount of bubbles in an area at one time, and the mean area transit time. Depending on microbubble location, they travel fast or slow. They travel slower in capillaries. In an in vitro model they observed that the amount of pressure that results in BBB opening correlates to the microbubble density. In human clinical trials, they are trying to create a biomarker for microbubble distribution that correlates contrast-enhanced imaging with perfusion MRI.

8 Question to Dr. Prada

Could you see differences in the rim of the tumor versus brain tissue using the microbubble approach?

The microbubbles enhance the bulk of the tumor and there are no large differences observed between the rim of the tumor and healthy brain tissue.

9 Question to Dr. Pouliopoulos

Were you able to spatially correlate neurogenesis with microglial activation?

They did not perform concurrent experiments looking at microglia with neurogenesis; they looked at astrocytes, which were clustered. They speculated that the immune response was involved with the observed neurogenesis.

10 Question to Mr. Gambin

How could the acoustic lens paradigm be scaled up for use in humans? Would there be different lenses for each location or one lens that negates the skull as it is moved?

In humans, the plan is to make one lens that can reach a large area of the brain with a single sonication to create a 3-D hologram, for example, treat the entire hippocampus.

11 Question to all

Please discuss the translation of your work given that the FDA has set limits on the microbubble dose for humans.

Dr. Pouliopoulos: The frequency has to be reduced to create a greater expansion of microbubbles.

Dr. Prada: Using microbubbles for imaging with ultrasound, there is an unpredictable variation in humans when using the same dose in different people. Infusion administration is better for microbubble administration to create constant levels.

.

Blood–Brain Barrier Opening—Other

Oral Presentation Q&A

MODERATORS

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

Richard Price | University of Virginia

SPEAKERS

Catherine Gorick | University of Virginia

Transplantation of exogenous mitochondria after ischemic stroke via FUS-mediated BBB opening

Yutong Guo | Georgia Institute of Technology

Characterization of nucleic acid nanomedicine delivery in brain tumors with microbubble-enhanced focused ultrasound at subcellular resolution

Robin Ji | Columbia University

Acoustic cavitation dependent immune response to FUS-induced blood-brain barrier opening

Alexander Mathew | University of Virginia

ScRNA-seq reveals FUS pressure dependent enrichment of transfected cell populations and their differential transcriptional responses after BBB opening

Transcriptomic response of brain tissue to focused ultrasound-mediated blood-brain barrier disruption depends strongly on anesthesia

Ying Meng | Sunnybrook Research Institute

MR-guided focused ultrasound trastuzumab delivery for intracranial metastases in patients with Her2-positive breast cancer

Sophie Morse | Imperial College London

Rapid short-pulse sequences deliver drugs across the blood-brain barrier with a low level of microglial activation and a low amount of blood-borne proteins released into the brain

Mehmet S. Ozdas | University Children's Hospital Zurich

Recurrent micro-seizure like activity following focused ultrasound and microbubble induced blood-brain barrier opening

Jerzy Szablowski | Rice University

A viral vector engineered for improved focused ultrasound BBB opening gene delivery.

1 Question to Dr. Gorick

How soon following the stroke were the mice treated?

The mice were treated 2 to 3 hours post-stroke and they will study treatments at later time points in the future. They have also considered performing the treatment after tissue plasminogen activator (tPA).

2 Question to Dr. Guo

Could the size-dependency of the nanoparticle be translated to other nanoparticles?

The model was to characterize the system of the brain microenvironment for nanoparticle delivery. They used mathematical modeling to optimize the nanoparticle, but it has not yet been tested. They hypothesize that 50 nM is the optimal size to use with FUS and BBB opening.

3 Question to Ms. Guo

How was the charge of the nanoparticle integrated into the model?

They did not account for the electrostatic charge in the model, but it was accounted for by the electrostatic hindrance in the medium.

4 Question to Dr. Ji

The cavitation dose seems dependent on the local population of microbubbles. How would you use the controller for changes in density or focus?

They did not vary the concentration of microbubbles but hypothesized that with a lower dose, the sonication time would increase in duration. If the microbubble concentration were changed, the FUS sonication duration would change.

5 Question to Mr. Ji

How would you know if you were in an area with low vascular density and whether the low dose was a result of vascular density or low-pressure amplitude?

This is a downside with passive cavitation detectors (PCDs); they cannot identify the signal location. They will also combine this with passive-cavitation imaging to create 3-D images that would allow further identification of the signal location.

6 Question to Dr. Mathew

Were the microglia consistent with a pro-inflammatory phenotype?

The genes were related to inflammation, such as CD68; there were no clear pro- or anti-inflammatory phenotypes. Interestingly, the transcripts overlapped with gene profiles associated with the resolution of inflammation after traumatic brain injury in mice. The time point under investigation was 48 hours after FUS and activated microglia would be expected to be returning to resting state after that amount of time had elapsed.

7 Question to Dr. Mathew

Were there any changes with microbubbles and FUS and how might that relate to clinical trials? Patients may be receiving pain medications, and could this affect any outcomes?

They could not perform BBB opening without anesthesia. Anesthetics are known to affect the vasculature and the baseline inflammatory response, and this is also true for pain medication. This is something to consider in the context of clinical trials.

8 Question to Dr. Meng

When would the antibody trastuzumab be injected (before or after BBB opening) and why was that decision made?

Drug was injected immediately before BBB opening because they are aiming to have the highest amount of drug in circulation during sonication. They hypothesized that there is a fast phase of leakage immediately after BBB opening that might increase the amount of drug entering the brain.

9 Question to Dr. Morse

Did they look into acoustic emissions during short pulses versus longer bursts? Were there any differences in energy distribution? Will the short-pulse approach allow the delivery of smaller particles such as proteins or viruses?

They had passive cavitation measurements and passive acoustic mapping. In terms of energy distribution, they see higher energy with longer pulses and closer to inertial cavitation with the longer pulses. This does not occur with short pulses. They are currently investigating the size of particles and will try to deliver 100 nM liposomes. Larger particles can be delivered, but the sequence has to be optimized to get larger molecules across the BBB.

10 Question to Dr. Ozdas

Concerning the studies being performed at 2.5 MHz: Have these experiments been repeated at frequencies closer to clinical usage?

They have not done these experiments. However, they expect similar results at lower frequencies.

11 Question to Dr. Szablowski

What are the properties of the viral vectors that are optimized for use with BBB and FUS that make them better for use in this setting and for transfecting neurons?

This was unknown. They make vectors with random mutations and then select a subset based on experimental observations. Mechanistic studies have not been carried out. They are seeking funding for experiments to find vectors that can work in multiple species.

12 Question to Dr. Szablowski

Synapsin was used exclusively to derive the promotor. If they attempted to target a different type of cell, astrocytes for example, with a different promoter, would the same kind of viral vectors show efficacy?

Looking at these differences might allow them to determine if it was transfection-related or passage-related. Dr. Szablowski hypothesized that their research seems to indicate that the viruses are selective for neurons, which means they might find that there are different viruses that select for different cell types.

13 Question to Dr. Morse

A recently published paper came to the opposite conclusion. What were the differences between these studies that might account for this?

The main difference was the microbubble dose, and that they have not tested their model with a clinical dose of microbubbles. Dr. Morse hypothesized that the higher dose will not lead to the same benefits that a rapid short-pulse (RaSP) sequence can give.

14 Question to Mr. Ji

Were there markers of astrogliosis and microgliosis in the array and were they significantly changed?

They were not part of the panel. Work is currently underway specifically looking at markers of the inflammatory response following BBB opening.

15 Question to Dr. Meng

Concerning patient recruitment for the trastuzumab study: Clinicians are aggressively treating recurrent metastasis with gamma knife and there are many additional ongoing clinical trials for breast cancer.

Patient recruitment has been slow. Patients that show interest are those that do not have very many options. Dr. Meng recommended that having a good working relationship with a radiation oncologist is also helpful for recruitment.

16 Question to Ms. Guo

Was there a reason for a timing delay of 8 hours between nanoparticle injection and BBB opening?

The injection of nanoparticles occurred immediately after BBB opening, and the animals were sacrificed 8 hours after the procedure. The timing was based on in vitro studies for the time point when consistent uptake occurred.

17 Question to Dr. Mathew

Concerning anesthesia crossing the BBB without FUS: Could enhancement of local delivery of anesthesia be influencing their results?

There is evidence that this could be occurring, but it is still an active area of research. There is ongoing research into which anesthetics cross the BBB most efficiently and what the distribution looks like. Anecdotally, the FUS-treated mice take a little longer to wake up.

.

Drug Delivery

Other Oral Presentation Q&A

Presentations highlighted the use of FUS for drug delivery. Preclinical studies investigated the use of FUS in combination with thermosensitive liposomes and nanoparticles, a cavitation-enhanced drug delivery system, passive acoustic mapping for spatial selectivity, and brainstem delivery of intranasal agents.

MODERATORS

Holger Grüll | University of Cologne

Sasha Klibanov | University of Virginia

SPEAKERS

Avinoam Bar-Zion | California Institute of Technology

Acoustically detonated biomolecules for targeted and genetically encoded cavitation

Juan Daniel Castillo Gomez | University Hospital of Cologne

Liposomal drug delivery of doxorubicin and cisplatin using MR-HIFU in a large animal model

Christian Coviello | OxSonics Therapeutics

Validation of SonoTran®: A cavitation-enhanced drug delivery system

Chulyong Kim | Georgia Institute of Technology

Ultrasonic thermal stress promotes acute changes in the transvascular transport dynamics in brain tumors and promotes targeted delivery of chemotherapy encapsulated in heat sensitive nanoparticles

Ali Mohammadabadi | University of Maryland School of Medicine

Lower interstitial fluid pressure and enhanced delivery and penetration of nanoparticles in solid tumors using nondestructive pulsed focused ultrasound

Cameron Smith | University of Oxford

Improved monitoring of ultrasound-enhanced drug delivery by passive acoustic mapping with spatial selectivity

Dezhuang Ye | Washington University in Saint Louis

Focused ultrasound-mediated brainstem delivery of intranasal administered agents

Yuana Yuana | Technical University of Eindhoven

Extracellular vesicles combined with microbubble-assisted ultrasound for drug delivery in cancer

Claire Wunker | Lunenfeld-Tanenbaum Research Institute

Magnetic resonance guided high intensity focused ultrasound generated non-invasive hyperthermia releases thermosensitive doxorubicin in a rhabdomyosarcoma murine model

1 Question to Dr. Bar-Zion

What was the blood circulation time for proteins, and were any immune effects observed?

The original gas vesicles only circulated for a few minutes. Recently, advances using various coatings on the particles resulted in around 30% of the gas vesicles still circulating in the blood 2 hours after treatment. The structures seem to evade the immune system.

2 Question to Dr. Bar-Zion

Were the particles targeted?

The gas particles can be targeted, but they can also be expressed by genetically encoding the proteins to bacteria or mammalian cells and following those pathways into the tumor. If immune cells are used, they would need to be extracted, modified, and replaced in the patient. The application for this would be to look at the immune response and the ability to activate cavitation.

3 Question to Dr. Bar-Zion

Were these particles extravasated?

There were a variety of gas vesicles, and the particles smaller than 100 nM can be extravasated.

4 Questions to Dr. Coviello

At 450 nM was any extravasation from the blood vessels expected? Also, given the large size of the particle, does the spleen filter the particle out of the bloodstream?

Extravasation occurs, depending on cell type. Some of the particles are filtered by the spleen, but they are also found in the target tissue (liver). For a standard human dose, cavitation can be sustained for up to 1 hour.

5 Question to Dr. Castillo Gomez

Why were two short hyperthermia treatments better than one long treatment?

The two hyperthermia treatments were performed to determine the optimal timing for FUS, and to use fewer animals. The experiments showed that higher concentrations of drugs were achieved with earlier time points. Longer treatments would lead to the temperature becoming more unreliable.

6 Question to Dr. Castillo Gomez

DPPG2 liposomes are new developments. Please describe their properties in greater detail.

DPPG2 is a novel lipid. The lipid has a melting point of around 42°C, which is perfect for hyperthermia treatments. The liposomes are stable at normal body temperature with little leakage of the treatment agents. There were 15% to 20% of circulating liposomes still in the bloodstream at 180 minutes after initial treatment.

7 Question to Dr. Kim

Please comment on heating near the skull.

Temperature mapping showed heating throughout the skull. Before deciding on a frequency, the researchers had already optimized the procedure to maximize treatment of the focal area.

8 Question to Dr. Kim

Concerning the clinical translation of this procedure: Is it feasible to perform drug delivery without overheating the skull?

It is possible. When treating humans, skull aberration corrections will be performed. They have not carried out any simulations with human skull but will likely do so in the future.

9 Question to Dr. Mohammadabadi

How is IFP related to IFV and can enhanced delivery be attributed to a pressure-based convective effect or diffusion due to a lower hydraulic pressure?

Different parameters are involved in increasing interstitial fluid pressure in the tumor.

Research has shown elevated pressure from the periphery to the center of the tumor. They hypothesized that it is a mechanical effect.

10 Question to Mr. Smith

Do you expect the linear relationship to apply to other types of therapeutic agents such as small molecules and viruses?

They would expect a linear relationship between the delivery and the cavitation dose.

However, just because there is a linear delivery ratio, it does not mean there would be a linear relationship for efficacy.

11 Question to Dr. Wunker

Why was the treatment volume much smaller than the volume of the tumor, and was the entire tumor excised?

The entire tumor was excised, and the reported drug average was for the concentration in the entire tumor volume. They accounted for tumor size in their analysis and found no statistical difference in tumor size between the treatment groups.

12 Question to Ms. Ye

Please describe the microbubbles used in the study.

The microbubble was homemade and measured 4 to 5 μM .

.

Drug Delivery

Panel

MODERATOR

Christy Holland | University of Cincinnati

PANELISTS

Costas Arvanitis | Georgia Institute of Technology

Overcoming the vascular, interstitial, and cellular barriers to drug delivery in brain tumors with FUS

Raag Airan | Stanford University

Ashish Ranjan | Oklahoma State University

Enhancing focused ultrasound-mediated delivery and penetration of doxorubicin in solid tumors using temperature sensitive- and bubble-based liposomes

Tyrone Porter | University of Texas at Austin

Leveraging ultrasound and stimuli-responsive particles for triggered drug delivery

Mikail Shapiro | California Institute of Technology

Talking to cells: Using focused ultrasound to turn engineered cells into remote-controlled theranostics

Yashar Kalani | University of Virginia

Costas Arvanitis discussed FUS-mediated mechanical stress that can promote increased BBB permeability, interstitial transport, and endothelial cell membrane permeability. FUS-mediated thermal stress promotes increased BBB permeability and triggered drug delivery.

Ashish Ranjan presented data suggesting the feasibility of combining ultrasound-guided FUS with low-temperature-sensitive liposomes (LTSL). Ultrasound-guided FUS for drug delivery is cheap and cost-efficient, and the speed of imaging is faster with an ultrasound-based method. LTSLs can improve drug penetration depth and penetration.

Tyrone Porter presented on the combination of thermosensitive liposomes and FUS. MR thermometry was used to monitor heating to create a pulsing scheme for tumor treatment with doxorubicin. Clinical trials are underway to assess the efficacy of this treatment strategy. Dr. Porter also discussed the use of FUS with pressure-sensitive particles, which were investigated using siRNA delivery. This method could be used to deliver a variety of therapeutics.

Mikail Shapiro presented on nanoscale devices that are based on cells. The team investigated making molecular buoyancy devices, i.e., gas vesicles. These biosensors have been used in combination with ultrasound for imaging purposes. The gas vesicles can act as seeds for cavitation that eventually result in large mechanical effects. The team is also working on gas vesicles that can be acoustically detonated.

1 Question to Dr. Arvanitis

Was there skull-heating-associated damage confirmed by MRI or hematoxylin and eosin (HE) staining?

The original experiments were carried at 1 MHz and skull heating occurred. Mathematical modeling was used to identify optimal transducer properties. They found that 1.6 MHz was the optimal frequency in mice to deliver therapy without tissue damage.

2 Questions to Dr. Arvanitis

Does hyperthermia cause vascular dilation, and was there vascular leakage as a result? Where is the microbubble the most effective?

They do not think the effects are thermal, but hyperthermia could increase the amount of drug that penetrates the tissue. They hypothesized this because drug penetration is a property of the drug and the target. For example, in mice, the pore size in brain tissue is 60 nM, and particles larger than that will not penetrate very deeply. There is a great deal of research on nanoparticles, which can help design particles with high and selective uptake by the target of interest.

3 Questions to Dr. Ranjan

How is the temperature controlled using the echogenic LTSL? Was the hyperthermia region covering the entire VX2 tumor?

The experiments were carried out in mice using an ultrasound-guided system, so there was no real-time thermometry available. The experiments were optimized using a set of parameters assuming that the temperature at the site of heating was 40° to 42°C. For VX2, MR thermometry was used to heat a portion of the tumor.

4 Question to Dr. Ranjan

What is the circulating time of the echogenic liposomes?

The pharmacokinetics were similar to LTSL, but they do not know how long the bubbles last in circulation. Heating occurred over 60 minutes in a sequential manner. There was also a sequential increase in drug delivery in the target regions suggesting that the bubbles were retained over a 1-hour period.

5 Comment to Dr. Ranjan

The immune response was an interesting observation and suggests partial treatment of the tumor may cause an immune response.

The immune response caused them to change their focus as a research group to look not only at drug delivery but also at how the immune system responds to the microbubble treatment. Nanobubbles do not cause cavitation but rather mild cellular stress that translates into an immunogenic cell death. They observe damage-associated molecular patterns and translocation of intracellular proteins; these may assist in an antitumor response.

6 Question to Dr. Porter

Have you measured drug release?

They have not measured drug release. They focused on leveraging bubble dynamics to optimize delivery. There is some published data on this topic from other research groups.

7 Question to Dr. Porter

When there is a phase change from a droplet to a gas bubble, there is an efficient degassing of the solution around the bubble. Have they looked at this in their experiments?

This could be used to scavenge oxygen. This might have potential uses in cancer, where the blood is deoxygenated to starve the tumor with an ischemic response. It might be interesting to look at this more deeply.

8 Question to Dr. Shapiro

Concerning the use of the 670 kHz frequency, why was this chosen?

Gas vesicles were used as the nucleators of bubble formation. This frequency was found to be more effective for bubble formation compared with higher frequencies. The gas bubbles are intended to be used for both therapeutic delivery and for diagnostic imaging purposes. The team discovered that at imaging frequencies (3 MHz or higher), there is no cavitation behavior from the bubbles.

9 Question to Dr. Shapiro

Did you investigate any of the cellular effects or biological responses?

They have used standard tools such as optical microscopy. Their research is focused on therapeutic effects such as a purified gas bubble targeted to a specific cell (such as a cancer cell). In this case the team looks for evidence that the cell was sonoporated using propidium iodide. When a cell is genetically engineered to express the gas bubble itself and essentially explode, the team uses assays to look for viability and to look for release of intracellular payload. When the two techniques, purified gas bubbles or genetically engineered cells, are combined to disrupt tissue in vivo, histology is used to look for effects of the disruption.

10 Question to Dr. Kalani

Please describe your work. Is the interest in using FUS to deliver mitochondria or therapeutic agents?

His research interest is in finding additional treatments for stroke. Mitochondrial dysregulation is known to be disrupted and lead to further injury following the initial ischemic insult. The hypothesis of the study was whether delivery of exogenous healthy mitochondria with FUS could rescue cells in the penumbra.

11 Question to Dr. Airan

Please describe your work.

He works on drug-carrying nanoemulsions. Phase-change particles were stabilized, resulting in a loss of phase-change properties. The particles are ultrasound-sensitive and release their cargo in the presence of ultrasound. Proof-of-concept work has been carried out in vivo. The current work is focused on the clinical translation of the system. The mechanism of drug release from the particle is unknown, but it is under investigation with high-speed optical imaging. So far, they have not observed a phase change, micron-level bubble formation, or acoustic backscatter. They hypothesized that there is a mechanical transformation occurring in the ultrasound field resulting in porosity that allows drug to escape the particle.

.....

Fireside Chat

Gene Therapy

Nathalie Cartier-Lacave, MD

Asklepios BioPharmaceutical, Inc. (AskBio)

Natasha Sheybani, PhD

Focused Ultrasound Foundation and Stanford University

In this fireside chat, Dr. Sheybani, a newly minted PhD studying the use of focused ultrasound to deliver gene therapy, interviewed Dr. Cartier-Lacave, a physician and gene therapy pioneer to learn about the current and future intersections of the two technologies. The two scientists discussed how gene therapy works, how it is different from delivering other small molecular agents, and how it only requires one therapeutic application to be effective.

Dr. Cartier-Lacave is currently using or studying monogene and multigene therapy for the treatment of Alzheimer's, Huntington's, and Parkinson's diseases. Huntington's, which is monogenetic, and Parkinson's, which is more complex, are both primed for translational studies. Two major challenges in gene therapy that must be overcome are manufacturing clinical-grade therapeutic viral vectors (called capsids) and improving the tools that are used to deliver the gene therapy vectors—especially across the blood–brain barrier (BBB). Furthermore, specificity of delivery is essential for safety and effectiveness. When asked about nonviral gene vectors, Dr. Cartier-Lacave said that liposomes and exosomes are showing promise for safety, specificity, efficiency, and scalability. She added that it is important to avoid generating an immune response when delivering gene therapy.

Focused ultrasound is likely to have a role in simplifying the process for gene delivery across the BBB and making it more efficient and specific. The focused ultrasound parameters that are currently being used to open the BBB are fairly simple, low-intensity, and transient in nature. Dr. Cartier-Lacave said that one session of intravenous gene delivery combined with noninvasive, nontoxic, low-intensity focused ultrasound would improve localized delivery in the brain for Parkinson's and Huntington's, but that a more diffuse delivery method could expand the therapy to Alzheimer's and other genetic diseases. There is an unmet clinical need for both approaches. Importantly, the use of focused ultrasound is likely to decrease the amount of viral vector needed to deliver the therapy, thus decreasing its currently high cost. Researchers, physicians, industry, patients, and disease-specific advocacy groups have been working together to find ways to reduce the cost of gene therapy and make it available to the small numbers of people living with rare genetic diseases. Dr. Cartier-Lacave noted that the image guidance used with focused ultrasound should help with the specificity needed for gene delivery, but anything that simplifies guidance, such as neuronavigation, is critical.

When asked what inspired Dr. Cartier-Lacave to work in the field of gene therapy, she shared that her love of medicine and research, together with her father's work as a biologist, inspired her desire to develop genetic solutions for diseases. She became involved in the field as soon as gene vectors had been developed.

• • • • •

Miscellaneous Indications

Oral Presentation Q&A

MODERATOR

Wladyslaw Gedroyc | Imperial College Healthcare NHS Trust

SPEAKERS

Torsten Bove | TOOsonix A/S

High frequency HIFU—A new modality for clinical dermatology

Chris Childers | Virginia Polytechnic Institute and State University Carilion School of Medicine

Focused ultrasound biofilm ablation: Investigation of histotripsy and particle-mediated histotripsy for the treatment of catheter-associated urinary tract infections (CAUTIs)

Wojciech Kwiecinski | Cardiawave

Non-invasive focused ultrasound therapy of calcific aortic stenosis: First-in-man study

Narendra T. Sanghvi | Focused Ultrasound Foundation, SonaCare Medical, LLC

Phase I/II clinical study using low energy focused ultrasound (LoFU) in addition to stem cell for the treatment of peripheral arterial disease

Gil Dubernard | Hospices Civils de Lyon – LabTAU

Transrectal high-intensity focused ultrasound (HIFU) for the management of rectosigmoid deep infiltrating endometriosis: Results of phase I clinical trial

1 Questions to Mr. Bove

Tell us about the 20-MHz probe. Might the technique replace surgery? At what temperature does the probe operate?

The probe was made in-house and can go down to about a centimeter in depth. It can be used for basal cell carcinoma, sarcoma, conditions in same family as warts, etc., including benign conditions. They can be treated with a single pass, or with a deep probe. It could replace surgery.

There is no temperature monitor inside the probe. At the focal point, temperatures reach 70° to 80°C, but on the surface the temperature rises very little.

2 Questions to Mr. Childers

Do biofilms constitute a bacterial surface? How often do you have to repeat the procedure? Is the procedure feasible for other than urinary catheters? Do you risk seeding infection distally around the body with this treatment?

They engulf the bacteria and attach to the biologic surface. Then the bacteria break off and go to other parts of the body where they hide from systemic drugs.

We repeat the procedure to move to the preventive side. We started with urinary catheters, but it can be applied to other catheters and to the vasculature as well.

There is some risk of seeding infection elsewhere, but that risk is the same as for removing a catheter. We need to compare removing the catheter with treating it.

3 Questions to Dr. Kwiecinski

You target the aortic valve and transcatheter valves. How difficult is it to target the aortic valve? MRI is performed before and after to see silent sequelae?

Targeting the aortic valve is classic for diagnosis. The valve is not so mobile, and the disease process helps target it.

Yes, MRI is performed before and after. Debris could come from the valve and calcifications could be embedded within the valve. They rarely occur outside the valve. The energy from FUS will not damage the valve. They have treated 20 patients so far; MRI detected no abnormalities. Qualitative tests on performance of patients showed no deterioration after 1, 3, and 6 months.

4 Questions to Dr. Sanghvi

This is an area where patients are often hopeless. Do you treat the musculature around the valve or just the surrounding tissue? Have you tried larger vessels?

We enter 5 to 10 sites on the vessel, depending on its length. We have only tried larger vessels below the knee.

So far we have stabilized patients, but we may be able to go beyond stabilization. We have only five patients per group, so we don't have a good understanding of regrowth. More imaging would help us see if the patients' condition has really improved.

Without anesthesia, the procedure is safe.

5 Question to Dr. Dubernard

How did you get the probe high enough to treat the sigmoid?

The location of the lesion was determined by MRI. Lesions started with external adenomyosis. The 3 mm between the mucosa and the rectal wall are cooled. Adhesions may be a centimeter or longer adjacent to the rectum. They have started a new study with 38 patients treating the area further forward to the rectal area except for adenomyosis.

We conclude that TR-HIFU therapy for posterior deep infiltrating endometriosis is feasible. It could be an interesting minimally invasive alternative to surgery for the treatment of rectosigmoid endometriosis if its efficacy and safety are confirmed.

• • • • •

Musculoskeletal Applications

Oral Presentation Q&A

Presenters discussed and compared treatments for bone metastases, osteomyelitis, and arthritis.

MODERATOR

Matthew Bucknor | University of California, San Francisco

SPEAKERS

Harshini K. Ashar | Oklahoma State University

Feasibility of treating implant-associated osteomyelitis with focused ultrasound and antibiotic-laden thermally sensitive liposomes

Joe Baal | University of California, San Francisco

Magnetic resonance-guided focused ultrasound for painful bone metastases: A pooled meta-analysis of 33 studies with 1082 patients

Alessandro Di Maio | Sapienza, Rome University

MR-guided focused ultrasound versus external radiation therapy for the treatment of pain in bone metastases, a multicenter open-label phase-2 clinical trial

William Chu Kwan | Hospital for Sick Children

Effects of MRgFUS boiling histotripsy combined with ablation in tendons: A pilot study

1 Questions to Dr. Ashar

Did you achieve increase in antibiotics along the bone interface? Can you go further? Can this technique be used for prolonged therapy? Does the artifact associated with the wires pose a challenge?

A long-term goal is to go further through better targeting and more drug delivery. We can better localize nanoparticles to the area of interest. A biofilm load occurs on the implanted metal wires and greater killing—greater bactericidal effect—was found on the wires than on the bone.

A goal is to decrease the number and frequency of treatments to make the procedure clinically relevant. A biofilm can be complex. Because this is an FUS-guided treatment, artifacts were not considered.

2 Question to Dr. Baal

Certain cancer types, e.g., breast, prostate, renal cell, and lung, metastasize to the bone. Grade 3 toxicity is rare. What types of bones fractured?

We could not determine that, but the data set may be skewed. Future studies of particular types of bones are needed.

3 Questions to Dr. Di Maio

Was the FUS procedure performed in one session or do some patients need repeat treatments? How many sessions of radiation did that set of patients receive? Was there a difference in types of tumors between the two groups? Do different types of metastases respond differently to FUS? Is there a difference in survival?

One session of FUS was needed to confirm the location. The aim was for a single dose of radiotherapy. Breast cancer was the most common, followed by lung cancer. Their metastases appear differently on MRI. If the surface is not eroded, in prostate cancer if we treat the tumor, we can reduce the size of the tumor, which has some global effect. Sensations of radiotherapy were much lower in FUS. Quality of life, morbidity, and survival all improved over the 12 months of the study, but more studies are needed.

4 Questions to Dr. Kwan

Did you monitor cavitation from boiling histotripsy from three different peak pressures? What is the time lag between boiling histotripsy and ablation? Can this procedure be used for preventive and palliative treatment?

We did not monitor cavitation but calculated the pressure that would induce the cavitation. Monitoring cavitation during treatment might produce a more localized effect.

The sequence of events is time-dependent as are most effects of histotripsy. The optimal sequence occurred within 5 seconds.

At the onset of contraction, we splint them for 22 hours per day, but that is not really effective and it also creates pressure ulcers, and physiotherapy is painful. Antispasmodic medication is used, but that is more palliative. Once contracture has happened, the treatment is surgery to slice the tendon, but contracture will return.

.

Musculoskeletal Applications

Panel

MODERATOR

Pejman Ghanouni | Stanford University

PANELISTS

Matthew Bucknor | University of California, San Francisco

Magnetic resonance guided focused ultrasound: Thermal ablation of desmoid tumors

AeRang Kim | Children's National Hospital

Applications and challenges of HIFU for pediatric sarcomas

Arik Hananel | FUSMobile Inc.

Focused ultrasound for arthritis

Joanne Tuohy | Virginia–Maryland College of Veterinary Medicine

Veterinary applications of focused ultrasound techniques as a comparative model

Matthew Bucknor from the University of California, San Francisco, studied benign but locally aggressive neoplasms, which can be sporadic or familial and often recur. Surgery is not the ideal treatment, whereas FUS is noninvasive and involves no ionizing radiation. FUS was used to treat desmoid tumors in 15 patients; 63% of tumors were removed and for all, pain scores decreased. Challenges include: 4- to 5-hour treatments, intra-procedural monitoring, strategies for preoperative planning, best practices when tumors are near critical structures, optimal continuation therapy/treatment synergy, and access. A randomized clinical trial is needed, as well as resolution of regulatory issues.

AeRang Kim from Children's National Hospital reported on treating pediatric sarcomas in which complete ablations are needed. This team tried drug delivery with hyperthermia and ablation, guided by high-intensity FUS (HIFU). Challenges include positioning and time spent to access the tumor.

Arik Hananel from FUSMobile Inc. discussed the potential of FUS to improve the existing standard of care for osteoarthritis where the joint is damaged, particularly the sacroiliac joints. Inflammation of these joints is mostly clinical and preclinical.

Joanne Tuohy from the Virginia–Maryland College of Veterinary Medicine discussed veterinary applications of FUS techniques in dogs as a comparative model. There are two ongoing studies in dogs of HIFU and histotripsy as treatment options. After HIFU, tumors were resected. Results will be used to advance comparative oncology research and to improve treatment for both humans and dogs. Osteosarcoma is similar in dogs and in humans.

1 Questions to Dr. Bucknor

How do you work around structures like nerves? Are you treating tumors that encase the nerve or are next to it?

Usually the tumor is next to the nerve. First, we get good visualization and then mark the location on software. If the nerve is encased, surgery cannot be used. We want to decrease

pain and increase range of motion. FUS is a good management technique. The percentage of ablation varies from treatment to treatment; 63% was cited in a retrospective study. For large tumors we need the capability to perform ablation with larger or smaller sonications.

2 Questions to Dr. Kim

What device could allow better access? Are there additional markers to see whether the combination therapy is working?

Part of the answer is positioning of the patient and where the tumor is located. We are limited by the instrument and where the FUS transducer is located on the instrument. Most limitations to ablation are tumor location and whether they are near a biostructure. Adjuvant therapy is needed to get at the entire tumor.

For the primary outcome, we use traditional measurements, but that is not so good for ablation—malignant cancers grow quite rapidly. We are looking at biomarkers and at other sites if the patient presents with several sites. Currently, we look at outcomes in the traditional sense, but we need to do better. Keeping track of the volume of dead tissue is tedious, but useful.

Combination therapy being used is Thermodox with HIFU, and we are in preclinical trials to compare histotripsy with ablation.

3 Questions to Dr. Hananel

Is thermometry important for FUS? How long does denervation last?

Having a closed-loop modality allows us to optimize a predictable plan. But, closing the thermal feedback is expensive and can complicate the procedure and extend the treatment time, which increases the cost of the procedure. Bone is very predictable, so a closed loop may not be necessary.

They treated a patient after cement injection, and denervation seems to last as long and treat as well as ablation.

4 Questions to Dr. Tuohy

Can you compare histotripsy with HIFU in animals?

To compare methods, they studied the use of histotripsy on soft tissue sarcomas in dogs. They want to find a nonthermal method of ablation. They are treating a prescribed area, not the whole. There is good comparison between gross appearance, computerized tomography, and histologic sections. When treating close to bone, we got a much larger ablation zone. They are not using an active skin-cooling system. But, once they progress to treating the entire tumor, they would have to explore ways to prevent overheating.

• • • • •

Chronic Pain

Oral Presentation Q&A

MODERATOR

Michael Gofeld | Silver Medical Group Centre for Pain Care

SPEAKERS

Abdul-Kareem Ahmed | University of Maryland School of Medicine

Bilateral magnetic resonance-guided focused ultrasound thalamotomy of the central lateral nucleus for medically-refractory neuropathic pain

Bashar Badran | Medical University of South Carolina

MRI-guided transcranial (t) focused ultrasound to modulate pain thresholds in healthy adults: A double-blind, concurrent tFUS/MRI study

Stephen Alexander Lee | Columbia University

Modulation of pain in humans via ultrasound peripheral nerve stimulation

1 Questions to Dr. Ahmed

What was the patient's toleration? Were patients sedated?

These were the first patients treated. They were not sedated. Feedback indicates that there is a learning curve. It is valuable to have the patient awake to work out the timing. The frame is well tolerated and pain decreased by 50% or completely. The literature covers lesion production. Around the lesion is edema. The other issue is that some patients have continuous excruciating pain, whereas others' pain is episodic. They do better with thalamotomy, which is known.

The patients we see have many commonalities. It is important to distinguish the kind of patient you have and not the kind of disease. Patients may have comorbidities. Exclusion/inclusion criteria must be defined. Failed back syndrome seems to predispose the patient to failure, although one patient did improve. MRgFUS thalamotomy won't work for everyone, so patient selection is important.

The next trial may be for patients with central neurofibril pain or radiculopathy of the head or neuralgia refractory to any other treatments.

2 Questions to Dr. Badran

What is your clinical application of LIFUP? How long will the effect last? When treatment is delivered over 4-6 weeks, do you get a huge effect that persists? Are you considering other targets?

LIFUP, which is noninvasive outside the skin, can be used to treat depression pain. A transducer is attached using MRI to guide it. It is not ablative. The effects are delayed, but eventually they will be additive. The dose could be increased by treating on multiple days. How long the effect lasts is calculated based on prior work.

They are considering targeting the insula, anterior cingulate cortex, amygdala, etc. There are many pathways of pain.

3 Questions to Dr. Lee

What is the mechanism of action hypothesis? Do median somatosensory evoked potentials signal changes? Next step?

The consensus is that ultrasound peripheral nerve stimulation is more a mechanical effect. They are using single pulses, so there is no temperature accumulation, but there is increasing displacement of the nerve. They are considering measuring somatosensory evoked potentials in the future.

Next they plan to look at thermal neuropathic pain, but they need a suitable model for repeatable pain, so they are working with a neurosurgeon and repeating dosages.

.

Women's Health

Panel

MODERATOR

Gina Hesley | Mayo Clinic

PANELISTS

Young-Sun Kim | MINT Intervention Hospital, Seoul, Korea

MR-HIFU for uterine fibroid site success strategy in stand-alone intervention clinic

Matthias Matzko | Helios Amper-Klinikum Dachau

MRgFUS for uterine fibroids: Pregnancy

Martijn Boomsma | Isala Hospital

MR-HIFU treatment of fibroids: Pregnancy

Gil Dubernard | Hospices Civils de Lyon—LabTAU

High-intensity focused ultrasound, a key treatment for endometriosis and adenomyosis

Young-Sun Kim from the MINT Intervention Hospital, Seoul, Korea, described outcomes of their minimally invasive therapy (MINT) treatment of uterine fibroids in a stand-alone intervention clinic. Complete necrosis is important for the long-term outcome. They concluded that MINT is an effective and safe treatment if strict screening is applied with a multimodal collaboration approach.

Matthias Matzko from Helios Amper-Klinikum Dachau reported on magnetic resonance-guided FUS (MRgFUS) as a treatment for uterine fibroids for women who want to become pregnant. Between 2014 and 2017, they treated 247 patients of whom 31 tried to conceive and 18 became pregnant (68% success rate). The pregnancy rate was good, with a low abortion rate and a reduced cesarean delivery rate. MRgFUS is safe to use in women who desire pregnancy.

Martijn Boomsma from Isala Hospital reported on a pilot study of 87 women to compare magnetic resonance imaging (MRI) scans with the fibroid tissue itself. All had undergone multiparametric MRI to characterize uterine fibroid tissue types. They developed a three-step modified manipulation protocol beginning with MRI mapping. This can lead to shorter procedure times, improved recovery, and more effective treatment.

Gil Dubernard from Hospices Civils de Lyon—LabTAU presented results of using high-intensity focused ultrasound (HIFU) as the key treatment for endometriosis and adenomyosis. The procedure is safe, simple, and cost effective. Treatment can be repeated, or conventional surgery can be performed if need be.

1 Question to Dr. Kim

Do you look at fibroid type before recommending HIFU?

Fibroid type is most important and is based on phenotype or classification. Many other things must also be considered including location of fibroid, socioeconomic situation of the patient, and the patient's future plans.

2 Question to all

Where do you envision additional use of HIFU, e.g., breast disease as well as breast cancer? Which features did you select? Do you use deep learning or artificial intelligence?

Dr. Matzko: Normal diagnostic methods used to select patients.

Dr. Boomsma: Deep-learning methods are really important because they enable looking at data in a different way. He used a deep-learning algorithm to recreate non-perfusion volumes without use of gallium. If used consistently, the treatment can be followed as it progresses. If vessels become occluded, the procedure can be stopped, and it reduces treatment time by half. There are different diffusion patterns for occlusion versus regrowth.

3 Questions to Dr. Dubernard

Are future trials of HIFU in France planned? How many patients have endometrial wall implants?

Yes, we plan future trials for this type of treatment. The treatment is difficult with a high risk of complications. The patient leaves the hospital the day after the procedure. For locations other than the endometrial wall, the patient may still need surgery. They do not have the equipment to conduct this surgery. They tried another device, but not HIFU for that location.

4 Question to all

Do you use pretreatment medications?

Dr. Matzko: Highly concentrated estrogen for 6 months before the procedure to get the blood perfusion down; results have been promising, but the recurrence rate is high. They have treated about 150 patients. Diffuse endometriosis recurs very frequently. If it is diffuse, we can only lessen the symptoms for a short time.

Dr. Kim: Agree. Recurrence of endometriosis is more frequent than recurrence of fibroids. Recurrences may last several months to several years.

Dr. Boomsma: They have treated one or two patients with MR-HIFU, but reimbursement is difficult and more evidence is needed before he can say this is the treatment of choice. Not all women have isolated abdominal wall endometriosis; sometimes it is more diffuse. So this is really personalized medicine tailored to the patient.

5 Question to all

What medications are you using to enhance the treatment effect, especially for patients with Tanaka type 2 endometriosis?

Dr. Boomsma: Lupron (leuporelin) and carbetocin. They enable more effective delivery of the terminal dose and the patient reaches the desired temperature level more quickly. It is important to treat the patient quickly so the procedure is more cost effective. Therefore, logistics are important.

Dr. Matzko: Metalgin (acetaminophen or paracetamol) to aid uterine contraction and to decrease the blood flow. The amount of energy can be reduced 10% to 20%, which means a faster treatment time. But this comes from observation and not objective data. After many years of use, no side effects have been observed.

Dr. Kim: Oxytocin to contract the uterus. It decreases the energy and is effective for type 2 fibroids. Complications are rare; occasionally a patient has palpitations or headache.

Dr. Dubernard: Only contrast medium to follow the treatment. All patients are lightly sedated (“waking anesthesia”).

• • • • •

Friday,
November 13, 2020

Keynote Speaker

Omar Ishrak

Intel

The Role of MedTech in Driving Patient Outcomes



Omar Ishrak

Mr. Ishrak, who serves as the executive chairman and chairman of the board of Medtronic and chairman of the board of Intel, discussed focused ultrasound from a medical device perspective. Health care technology is a growth marker. Our quest for improved clinical outcomes will never end, so the progress of technology will go on, and growth in the medtech industry will never end. Focused ultrasound is a technology that is trying to improve clinical outcomes.

Medtronic's mission statement, "Contributing to human welfare by the application of biomedical engineering to alleviate pain, restore health, and extend life," is inspirational but also strategic. It can be translated as "A technology company dedicated to improving patient outcomes," and the same can be said for every medtech company. Medtech innovation has three distinct phases that should run in parallel across multiple therapy areas:

- Inventing new markets by creating and developing new therapies that result in new markets
- Continually innovating by enhancing the clinical outcomes and economic value of existing products
- Disrupting markets by bringing disruptive therapies into existing markets

Commercialization follows a four-step process, and each step is needed to scale a technology. The steps are: developing a working product, gathering clinical evidence, achieving regulatory approval, and establishing an appropriate payment mechanism. Medtronic's Solitaire X revascularization device is an example of this process. It is also important to make the technology the standard of care while establishing reimbursement to drive adoption while expanding into new markets. Expanding a new therapy can happen organically and inorganically over time. It takes focus to develop a technology, time to create the standard of care, and capital to sustain the momentum. Large companies have the resources to develop several products in parallel, but startups often do not.

From a medtech perspective, focused ultrasound needs committed clinical champions and partnerships with diagnostic imaging specialists. In general, focused ultrasound is outside the comfort zone of scaled medical device companies, which is a potential barrier. Focused ultrasound will scale with the community's commitment, creativity, time, resilience, and perseverance.

.....

Track A

This webinar examined the spectrum of commercial motivations and behaviors and how they have practical effects throughout a company's life cycle.

.....

Investor Ecosystem 101

Randy Castleman | Focused Ultrasound Foundation

Venture investors' commonalities include structure (limited partners, general partners, etc.) and incentives (management fees, carried interest, etc.). Their behaviors focus on return generation across an entire portfolio and add value to each investment. All need to produce revenue for the organization they serve within the constraints imposed on them. Increasingly active are non-traditional investors, including:

- Corporate venture capital (CVC) investors. CVC investors include high net-worth individuals, family offices, and multifamily offices.
- Private equity (PE) investors. PE investors include private equity funds, hedge funds, and mutual funds. Asset managers manage endowments, foundations, pension funds (public and private), etc.
- Asset managers. They are outsourced teams of investment professionals or chief investment officers (CIOs).
- Sovereign wealth funds, which contain money of nation states.

Corporations focus principally on generating revenue for their company. Incentives differ — they could be returns generated, strategic value generated, profits, interest, capital at risk, or career at risk. Capabilities differ depending on fund size, decision-making, and flexibility, etc.

The company owner needs to know whether he or she is dealing with the principal or an agent and what the returns and expectations are—a share in upside, financial return required or expected, nonfinancial returns, hold period, or portfolio considerations.

Capabilities include capital reserves, unilateral decision-maker or bureaucracy, existential risk, ability to assist your company, and ability to think or act creatively. Each has different outcomes, and the relationships can be long-lasting. Different investments have different incentives and different capabilities and goals.

.....

Navigating the Investor Ecosystem

MODERATOR

Patrick Edelmann | Focused Ultrasound Foundation

SPEAKER

Sumit Mukherjee | Bank of America-Merrill Lynch

The year 2020 has seen unprecedented fiscal and monetary stimulus, but unemployment is still high. At the same time, COVID-19 has generated enthusiasm for health care, so growth continues. In this year to date, medical technology is rebounding and significantly outperforming at a 10-year high in areas including neurovascular and vascular technology, robotics, stem cells, and ophthalmology. At the same time, medical devices and electronics are coming together. Noninvasive technology is speeding processes, which shortens procedure times and helps manage the cost of care.

Companies seek strategic acquisitions and investment opportunities. But not all money is the same. Strategic investment is not simply based on return on investment (ROI). Subsectors of companies are being identified while only 20% of the market is devising new products. Similarly, not all governance is the same. Investors need to think about corporate governance early in the process.

Partnerships are increasingly important, and with partnerships the personality of the investor is a major consideration. Beyond the money, can the investor help you expand your products and markets? Finding partners involves many things. Think about having an advisor on your board. Think about key steps that must be taken before you exit from the current business.

A management team can enable you to see the forest beyond the trees. All these aspects will matter beyond the actual product.

To avoid pitfalls, generally, simpler and cleaner means a better overall outcome. Having the right amount of capital is important, but a partner who precludes you from getting other partners in the future could outweigh the advantage of having cash immediately. Never lose sight of your mission.

The size of the market is the investor's first consideration. This goes hand in hand with clinical need. The financial profile of the company makes a big difference, but with the current market and need, there are many options. In 2020 US health care private capital markets made up about 40% of the total market.

.....

Business Models 101

MODERATOR

Jon Carlini | Focused Ultrasound Foundation

SPEAKER

Thomas Andreae | Bank of America-Merrill Lynch

Whether your company is selling a piece of equipment or a health care solution, it may present an opportunity for the customer to diversify, or it may be something from which the customer can make a lot of money.

- Equipment sale. Direct sale from the manufacturer to a health care facility can be an outright purchase or a purchase over time. Typically, the sale includes installation and maintenance, which transfers risk to the buyer. A direct sale may be to a leasing company and not to a doctor or a hospital.
- Operating lease (captive financing). This option requires the manufacturer to keep track of timing to either renew a lease or issue a new lease for upgraded equipment. The purchase price of equipment can be reduced by the customer's taking a share of the business.
- Revenue/risk share. The purchase price of the equipment can be reduced by taking a share of the business.
- Equipment as a service ("pay per click"). With pay per click, the customer is charged only for use of the equipment.
- Rental
- Services. There are business opportunities in servicing medical equipment.

Business models include time of cash receipts, equipment ownership, and customer budget type. For whatever model, you must first understand your customer. Namely:

- Identify the real decision-maker early.
- Be customer-centric (understand their business model and their values).
- Quantify your value (ROI) and substantiate your claims with research. Then convince the customer that you will deliver.
- Develop ancillary revenue streams, e.g., sell related services, sell disposables (unique to you) and spare parts, sell data.

• • • • •

Business Model Trends in the MedTach Industry

MODERATOR

Patrick Edelmann | Focused Ultrasound Foundation

SPEAKER

Jonas Funk | LEK Consulting

COVID has accelerated many existing trends. The Coronavirus Aid, Relief, and Economic Security (CARES) Act has helped, but more patient businesses will be forced to consolidate. Although the demands of COVID paused this trend to value-based care, we are moving in that direction.

The more expensive the technology or service, the greater the near-term challenge to finance it. Since COVID, many hospitals have been struggling—a third made money, a third broke even, a third lost money—and there will be pressure against outright equipment purchases. All the business models are advantaged to the larger, more scaled player. They include:

- Equipment sale. Buying upfront is the cleanest and easiest way.
- Capital lease (third-party financing or captive financing). This is not new, but more frequent. There are more equipment servicing and maintenance businesses; sometimes they offer free upgrades.
- Operating lease (third-party financing or captive financing)
- Revenue or risk sharing
- Equipment as a service (EaaS) (pay per use) or shared savings or performance-based pricing
- Rental
- Selling services

Technology, when answering customer needs, must reduce costs or improve care. A product is no longer sold directly to a doctor but to purchasing departments. To invest in marketing and corporate development, the keys are:

- Find strategic partnerships (funding, credibility, expertise).
- Get sufficient funding for a closely defined product, clearly describing what it does and for whom.
- Establish the right balance between customer-centric and product-centric models. Customer-centric is becoming the highest priority.
- Find appropriate commercialization and pricing models.
- Fundamental is identifying the customers you want to address

To break through, a small company must define the endgame early and build to it in a focused way. You need to know what third-party resources to use and when. This involves keeping informed by reading, research, and networking. Know what's happening in your ecosystem.

.....

Dancing with a Giant

Tips for Productive Relationships Between Startups and Corporates

MODERATOR

Patrick Edelmann | Focused Ultrasound Foundation

SPEAKER

Rafael Torres | Varian Medical Systems, Inc.

The medical technology industry is resilient: revenues are growing at about 7% annually. COVID set people back, but it also accelerated digital adoption. So, the business question is how to leverage that.

Trends that are becoming prevalent are evidence-based, e.g., data-driven, value-based care; remotely delivered medicine (telehealth, etc.); and robotics. Your solution to an unsatisfied need must be affordable and have a key benefit.

With multiple geographies, ambulatory centers capture more and more procedures. To narrow the options, focus development toward overlapping strategies whose purveyors might be interested in you. Optionality creates value. Then consider how that will translate to actions, e.g., intellectual property (IP) structure. You must be clear about where you are going to add value.

Follow the money. Investors will be interested in how your solution will benefit the problem, and how you are creating value in a way that is measurable. This combines cost-effectiveness with medical effectiveness. Things to consider early in the process include:

- Reimbursement
- Regulatory issues
- Deliverables and how they are being measure
- How the institution aligns with your objectives
- Corporate governance
- Distinguish investors from shareholders
- Differentiate between the revenue model and the business model
- Establish a treatment paradigm, i.e., a therapy plan, a plan system, a guidance system
- Allow customers to focus on what they are good at, i.e., understand your cust
- Ensure that your process is replicable

Attracting one of the giants to get a strategic investor is not about having the newest technology; it is about understanding your customer better than they do.

• • • • •

Exits

Considering IPOs vs Acquisitions vs Mergers

MODERATOR

Philip Keevil | Focused Ultrasound Foundation

SPEAKERS

Tim Berkowitz | InnovaHealth Partners, LP

Patrick Edelmann | Focused Ultrasound Foundation

InnovaHealth, a health care company, was drawn to medical technology because for the last 20 years there has been a dearth of capital and no equivalent to Silicon Valley, i.e., the field was fragmented. They saw an opportunity to identify companies that can add value to a lifetime of investment. It's hardware vs software—both have an important role and do not exist independently. Today the two fields converge. For example, implantable devices are part of proceduralization, accompanied by factors such as differentiated imaging or robotics. Products that assist in reducing the time that procedures take can improve health care and reduce health care costs.

Artificial intelligence and machine learning are elements of hardware and software that become part of the discussion. Investors should review philosophical strategies at all stages—early, mid, and late. This is an important set of meetings to convene with all who are involved to make sure your interests are aligned. Agree on important factors; you need to know about divergence upfront. Then either address the divergence or find other money. The issue of balance of power is an important one.

If there's money available that is compatible with your direction, it's wise to take it so you don't have to have the same discussion in 6 months or a year. Worry about dilution, but, most important, you should build your company and get off the fund-raising trail.

Philosophical strategy is all about creating a broad understanding of where you are going. Define the relative importance of corporate governance, board representation, and strategic discussions. Use capital to resolve conflict, e.g., doing a study or building out European representation. With enough money, you can do it all at the same time. Create a board that is respectful of the team that brought the company to where it is. For proper representation, you need to align investors with knowledge providers.

Mr. Berkowitz is skeptical about initial public offerings (IPOs) because the window opens and shuts. When you're ready, you need advice on what is available, whether that be a straight sale to corporate or an IPO. It may be better to take a corporate sale. Consider whether the business is strong enough to support itself in a public environment and the risks and rewards.

The distribution system is important. You want significant growth in the final years before the cash-flow break-even, and that means working with the right distributor community and having the right people in place. The direct method will be more expensive, but it gives the company greater control and obviates large payments to third-party distributors.

When avoiding pitfalls, the major question is whether to bring in outside investors or to go it alone. There are huge benefits to bringing in a knowledgeable, outside investor. An outside investor can be a source of information or a source of relationships that will help build the business quickly. It is well worth addressing these things as early as possible. Founders can be confident about their technologies, but not know the right questions to ask potential investor partners. You need the right valuations and the right team members.

.

FDA Town Hall

Greg Clement, FDA research physicist, Office of Science and Engineering Laboratories (OSEL), introduced the FDA town hall panel. He noted the role of the FDA in the regulation of devices through the Center for Devices and Radiological Health (CDRH) and research programs through OSEL that aim to accelerate medical applications for safe and effective medical devices

.....

How to Engage with the FDA

MODERATOR

Subha Maruvada | FDA Acoustics Engineer, Center for Devices and Radiological Health

SPEAKERS

Bennett Blumenkopf | FDA Medical Officer, Neurological and Physical Medicine Devices

Greg Clement | FDA Research Physicist, Office of Science and Engineering Laboratories

Matthew Myers | FDA Research Physicist, Office of Science and Engineering Laboratories

Adam Pierce | FDA Acting Assistant Director for Neurosurgical Devices, Office of Product Evaluation and Quality

Xiaolin Zheng | FDA Director, Division of Neurosurgical, Neurointerventional, and Neurodiagnostic Devices, Office of Product Evaluation and Quality

Questions to all:

1 The FDA should encourage the pre-submission process for investigational device exemption (IDE) applications and work together with investigators before initiation of an experiment. The FDA could include physicists to review applications.

The pre-submission process is not required but facilitates the approval process and is highly encouraged. From a clinical perspective, the pre-submission initiates a dialogue between the agency and clinical investigators and ensures that the study design and safety of the device is well understood by both parties. This relationship will minimize revisions during IDE submission and speed approval.

The pre-submission process allows internal teams at the FDA, clinical and nonclinical, to address questions about the application and communicate a unified message to the sponsor.

It is important to include physicists in the review process, as nonclinical considerations may arise. Technical and engineering expertise from physicists and electrical and software engineers is highly advantageous; these teams can provide additional resources and suggest methods for different requirements for investigators.

2 Can the FDA provide advice on breakthrough device designation applications for novel focused ultrasound (FUS) therapies? Specifically, how should sponsors prove they meet criteria 1 as “a more effective treatment option” when very limited clinical outcome evidence exists, and similarly for criteria 2 “offering significant advantage over existing approved alternatives”?

The breakthrough device designation is based on statutory criteria, criteria 1 being the most important to the FDA. Criteria 1 includes performance data about how the device provides a reasonably more effective treatment or diagnosis of an irreversibly debilitating or life-threatening condition, compared with currently available treatments or diagnostics used in this patient population. Criteria 2, supported by performance data in criteria 1, requires evidence about how the device represents a breakthrough technology if there are clear alternatives, how the device offers a significant advantage compared with current standard clinical practice, and that the device availability is in the patients’ best interests. Most review considerations are focused on breakthrough designation criteria 1, which consists mainly of performance data.

3 What is the percentage of academic laboratories applying for IDEs or investigational new drug applications (INDs) without the support of commercial partners?

The FDA does not track the submissions from different types of sponsors, but we can look at this data.

4 What are application requirements for a foreign company to conduct an IDE clinical trial, and is the only solution to have a US branch act as the sponsor?

A foreign company must have a US agent that acts as the sponsor. The US agent must fulfill all the responsibilities of a sponsor as explained in the IDE regulation.

Data from a foreign company can be reviewed by the FDA. However, the study patient population, methods, and site must meet the same regulations expected from a study conducted in the US. The study data and patient population must be relevant to US patients.

5 Given that ultrasound technologies are exploring new applications and can replace more invasive therapeutic options, can the FDA provide any guidance on how sponsors should develop a risk-benefit analysis and a risk management plan?

Novel US therapies will require an IDE application to legally conduct research in human subjects in the US.

The FDA reviews the comprehensive risk analysis plan within an IDE application and recommends the Institute for Clinical and Economic Review (ICER) standards 14971 as a guideline to write the risk management plan. The latest ICER 2019 version for applications of risk management to medical devices can guide sponsors in writing risk management plans, identifying all device and device use-related risks, and suggesting performance strategies to mitigate those risks.

The FDA requires the sponsor to have appropriate performance testing or risk mitigation before they initiate the study in the US.

The mechanism of action is important in the risk-benefit assessment of a device. FUS, being a definitive ablative approach, is superior to other techniques that are nonablative and adjustable over time.

6 Is patient preference taken into consideration as a criterion in risk-benefit assessment?

The FDA is starting to consider the patient perspective very seriously, and clinicians support its integration in risk-benefit analysis. Patient preference related to ease of use, ease of implementation, willingness to tolerate a certain level of risk in one procedure versus another, and other practical concerns are important considerations.

The patient perspective is helpful for individual device applications, but in the long run, it also provides a better understanding about what matters for patients and how the agency should review applications for the best interest of patients.

7 Does the FDA plan to move to a fully electronic submission process as opposed to currently hard and electronic copies?

The FDA has moved to electronic e-copy submission except for the company cover letter that continues to be required as a hard copy. Appropriate e-mail addresses that accept e-copies are included at the conference “FDA booth.”

8 Methods to perform in vivo testing of ultrasound focal accuracy, temperature increases, and energy at the point of target do not exist. FDA requires this information from sponsors, but there are no standards for practice or guidance.

It is important to know where the energy is directed, especially in an organ like the brain. The agency requires in vivo methods, yet these are not easily performed. For some devices, an in vitro approach might suffice, and there are techniques for doing it.

For example, if you are working with phantom-embedded thermocouples and the thermocouple locations are accurately known, it is possible to sonicate the phantom aiming for a marker and see how far you are. It is important to know the thermo location accurately.

The agency uses a phantom with micro-computed tomography (CT); this is a published technique and a reference is available. There are thermo methods that can be performed on animals, if the sponsors have access to MR (magnetic resonance)-thermometry.

In vivo methods are available, and the agency can provide more information about these techniques to interested sponsors.

9 Can an individual with a master’s degree in physics be a regulatory officer? Which courses are needed to advance an individual regulatory career?

Regulatory officers need to have good communication skills, be comfortable in a team-based environment, and understand the interdisciplinary aspect of decision-making at the agency. The FDA adopts a multidisciplinary approach in all decisions; therefore, being able to communicate with colleagues of different academic backgrounds is key.

Physics is an important discipline in the device regulatory world. More important than the academic discipline is the ability to transfer a specific knowledge to solve real-world problems and adapt new technologies to real-world practice.

The FDA does not offer regulatory courses, but there is a regulatory affairs professional certification. The FDA has a reviewer certification program for all new officers, and this course is constantly updated.

Regulatory work requires the individual to look at things differently from what is expected in the traditional health care profession setting

10 Does the FDA have guidance on how to establish a maximum therapeutic energy dose, an overall time duration allowed for histotripsy, how to measure the dose, output power intensity, spatial pulse average, or any other metrics?

There is no FDA guidance on how to establish thermodose and duration for histotripsy. The International Electrotechnical Commission (IEC) ultrasound device test measurements standards can assist in measuring histotripsy dose and output in HITU (high intensity therapeutic ultrasound) devices. The agency also relies on guidance from IEC Technical Committee (TC) 87 ultrasonics working groups 6 and 8, which deal with HITU devices as well as field measurement techniques for ultrasound fields.

These standards are IEC 60601-2-62 for safety of HITU devices and histotripsy. IEC 62555 and 62556 are for power and field measurements for HITU devices.

Histotripsy has unique field characteristics that are considered on a case-by-case basis. Current HITU standards are helpful for characterization of these devices; however, there is no consensus on densitometry yet.

The lack of consensus about mechanical dosing standards exists in the entire field and academia. The FDA recognized this unmet need and is working with IEC to develop standards.

11 How does the FDA plan to facilitate academic submissions

The FDA equally reviews submissions from large companies, sponsored investigators, individuals at academic institutions with a novel idea, individual developers of a novel device, and investigations for new products.

Most individual investigators don't have the company or sponsor support and face the complex submission process, and as such are strongly encouraged to go through the pre-submission process to be initiated.

Several academic institutions established a technology transfer or a patent office with dedicated staff to handle the regulatory aspect of a new device and assist individual sponsors.

12 Which individuals are considered qualified data monitors? When is a formal Data and Safety Monitoring Board (DSMB) required? Are there different requirements for pilot versus phase 2 or 3 studies, and for investigator versus company-initiated studies?

The National Institutes of Health (NIH) offers guidance that delineates when a full DSMB versus a single dependent safety monitor is needed. Single site studies only require an independent safety monitor not involved in the study to provide independent adjudication. Multiple site studies require a DSMB panel to coordinate and oversee safety reporting from all sites. There might be other considerations in the guidance.

OSEL performs regulatory research and can provide guidance. Investigators are encouraged to reach out to OSEL at the FDA for technical or general scientific questions related to research.

13 How does the FDA work with the Centers for Medicare and Medicaid Services (CMS) toward a streamlined approach to regulatory approval and reimbursement?

The FDA does not issue a final coverage decision; rather, it provides recommendations based on clinical studies that inform CMS coverage decisions.

The Center for Devices and Radiological Health (CDRH) has a dedicated “CMS group” that interacts with CMS. For CMS-related questions and to get reimbursement for clinical studies, investigators can contact the CDRH and get in touch with their CMS-support group.

.

The Power of Advocacy Organizations

Jessica Foley described the role and the mission of the Focused Ultrasound Foundation (FUSF) and its collaboration with MITA and AdvaMed, two leading advocacy organizations with expertise and relationships to address issues of patient access and roadblocks to device commercialization. The partnership between FUSF, MITA, and AdvaMed now includes 11 FUS companies that have made important efforts to increase awareness and speed the approval of ultrasound devices.

SPEAKERS

Jessica Foley | Focused Ultrasound Foundation

Patrick Hope | Medical Imaging & Technology Alliance (MITA)

Brian O'Connor | Advanced Medical Technology Association (AdvaMed)

1 Question to all

How can we work together to help remove roadblocks, enable access, and help companies work together?

AdvaMed and MITA members represent a full spectrum of organizations — from startups, small, and medium companies to large companies — in the advanced medical imaging market. The organizations’ primary focus is advocacy to increase awareness of the technology and the development of standards to ensure patient safety.

All FUS companies are encouraged to become members of MITA. Members can join reimbursement and coverage committees and provide input in the letters that the organizations send to the FDA and CMS. All members can participate in strategy discussions.

There will be a need to develop standards in the long term as the industry matures.

2 Question to Brian O'Connor

How is AdvaMed working with the foundation and FUS companies?

The FUSF has a large breadth of applications of therapies. One of the very effective tools developed by Jessica Foley is a one-page handout that shows all FUS therapies advancing across the timeline from approval to reimbursement.

AdvaMed ensures that small and big FUS companies are equally represented in the FDA, in government affairs, and in reimbursement committees. In addition to developing policy, AdvaMed works in advocacy and highlights efforts of the foundation.

One of the FUSF successful campaigns was the Capitol Hill “fly-in” program. This initiative allows members of FUS working groups, members of the foundation, patients, and providers to meet with members of Congress and White House staff.

Last march, the FUSF was promoting a new breakthrough designation pathway to eliminate the lag between FDA approval and CMS reimbursement for innovative medical device companies. Once finalized, the newly created Medicare Coverage for Innovative Technologies (MCIT) program will provide immediate coverage for breakthrough FUS technologies for 4 years, a big win for FUS companies.

Several companies are not familiar with the breakthrough designation, and FUSF does a lot of advocacy work with its partners and the federal government.

3 Question to Brian O'Connor

How has AdvaMed advocated for this breakthrough designation pathway, working with member companies on these efforts?

As part of the 21st Century Cures Act, the breakthrough therapy designation provides an accelerated pathway to approval of innovative devices. Once approved by the FDA, breakthrough devices will still have to be reviewed by the CMS, a process that takes 3 to 5 years.

The organization is educating member companies about innovative technologies and their positive impact on patients and disease burden. Initiatives such as the Capitol Hill fly-ins that allow physicians and patients to participate in workshops and meet White House officials, as well as joint letters from the foundation and letters to the editor, are necessary to close the gap between FDA approval and CMS reimbursement.

4 Question to Brian O'Connor

How did AdvaMed work with its member companies to address COVID-19 challenges and ensure success in this environment?

With COVID-19, the industry was forced to change overnight. There were shortages in personal protective equipment (PPE), ventilators, tests, and other life-saving devices. Medtech companies reorganized and shifted their structural alignments to resolve supply chain and sourcing issues for ventilators and pulled together to crowdsource. Companies collaborated to focus on COVID response with unparalleled dedication. Diagnostic registries were set up to gather data about supplies and testing availability across the United States.

Board-level committees formed and worked across three predominant areas: 1) the return-to-procedure for people who needed to go to the hospital and ensuring safe return to

hospitals for non-COVID patients, 2) continuing the diagnostic testing, and 3) protection of small companies that were affected in this process.

5 Question to Patrick Hope

MITA created the Back to Care campaign to encourage patients to return safely to testing including imaging and screening.

The COVID-19 pandemic had important repercussions on hospitals and the delivery of health care services. There was a decline in screening and CT imaging, and elective procedures were delayed. There was a shortage of health care resources and physicians due to clinic closures or layoffs.

Many patients delayed their annual screening. Missing diagnoses affect treatment and clinical outcomes. MITA created the Back to Care campaign, encouraging patients to return to care through testimonies of patients and physicians and sending letters to patients about the safety and the importance of diagnostic testing. This campaign made an impact on the levels of screening, and procedures have increased.

Ultrasound technique is an outpatient, noninvasive procedure that does not carry the risk of infection and does not compete with hospital beds. FUS does not use ionizing radiation and does not interfere or compromise the immune system, a real concern during COVID. Ultrasound testing is rising to healthy levels and continues to increase.

6 Question to all

How could the upcoming presidential election impact medtech innovation and the prevailing issues that FUSF is working to resolve? [The session was recorded prior to the election.]

Patrick Hope: If re-elected, President Trump will continue the conversation around supply chain issues, a necessary conversation. A Biden presidency means increased patient access, which is good for patients to get screening. As president, Joe Biden will continue to lead the cancer moonshot, a good opportunity for increased funding in cancer.

Brian O'Connor: Our organizations' work is bipartisan, and we must continue to highlight the work our companies do, tell our story, show the impact of the Back to Care campaign, and advance all forms of medtech.

.

Regulatory

Medical Devices and Combination Products

Daniel Schultz | Greenleaf Health, Inc

Daniel Schultz noted that FUS is an early-stage noninvasive technology that uses ultrasound to target tissue deep in the body without incision or radiation. High-intensity focused ultrasound (HIFU) technology has wide applications with great potential in medical care. FUS produces mechanical and thermal energy and has unique effects such as opening the blood-brain barrier and neuromodulation that offer great clinical promise. HIFU offers

novel functionalities such as cavitation, modulation, and opening of blood-tissue barriers. A single regulatory pathway is needed to ease the understanding of application submission and accelerate approvals.

Section 513(a)(2) requires the FDA to examine the safety and effectiveness of a device. Device classification is based on risks versus benefits and relies on valid scientific evidence. Premarket submission evaluations are risk-based, data driven, and focused on indications for use, technological characteristics, and performance.

Medical devices are divided into three regulatory classes based on levels of risks and controls needed to mitigate risks and provide safety and effectiveness. The classes range from Class I, simple devices exempt from premarket submissions, such as toothbrushes, tongue depressors, and over-the-counter products, to Class III, high-risk devices about which there is the least understanding of risk mitigation.

For Class II devices, or 510(k) products, the FDA has determined that risks can be controlled with a combination of general and special controls. Class II includes devices for electrosurgical cutting, coagulation devices and accessories, stimulator systems for esthetic use, and high intensity ultrasound systems for prostate tissue ablation. While these applications are for HIFU, functionality is very similar to radiofrequency, microwave, or other types of energy sources that ablate tissue. Examples include the Sonatherm 600 ultrasonic lesion-generating system indicated for ablation of soft tissue, Ultherapy indicated for localized heating for tissue coagulation and aesthetic purposes, and the Sonablate device indicated for ablation of prostate tissue.

Class III HIFU devices are subject to premarket approvals (PMAs), and they generally target specific clinical indications rather than superior functionality. Examples include the ExAblate 2000 system for ablation of uterine fibroid tissue in pre- or perimenopausal women with symptomatic uterine fibroids, with two subsequent PMAs; ExAblate for pain palliation of metastatic bone cancer;; and ExAblate Neuro for unilateral thalamotomy treatment of idiopathic essential tremor in patients with medication-refractory tremor.

Factors considered in regulatory determinations include 1) indication for use, 2) classification as a tool or treatment, 3) mechanism of action, and 4) use in combination with another drug or device. Key requirements for acceptance of clinical data include the applicability of data to the US population, similarity in the practice of medicine in the country, availability of acceptable patient protection, and availability of complete patient-level data.

Approval pathways, such as the breakthrough devices program, facilitate access to medical devices by expediting their development, assessment, and review while preserving the statutory and regulatory standards of safety and effectiveness. The MCIT program will allow accelerated reimbursement for FDA-designated breakthrough devices. Other programs include the parallel review and early payer program, whereby the FDA can invite CMS or private payers into the discussions with companies, ensuring data are presented to the agency for safety and effectiveness evaluations, and facilitating a more streamlined path for reimbursement and codes.

• • • • •

Medicare Reimbursement Pathways for FUS

Stephanie Kennan | McGuire Woods, LLP

Stephanie Kennan discussed the new proposed rule by CMS to 1) create a new pathway for breakthrough technologies, and 2) codify products as reasonable and necessary.

To be considered a breakthrough device, a product must offer a more effective diagnosis or treatment for a debilitating disease or condition, represent a breakthrough technology for which there is no approved or clear alternative, or be in the best interest of the patients. Coverage is only applicable for FDA-approved indications, and products not classified under specific “drug” or “device” Medicare categories are excluded from the pathway.

There are several pathways for coverage. Currently, coverage is obtained via national coverage through CMS. Additional pathways include local coverage decisions (LCDs) via regional Medicare administrative contractors (MACs), coverage through clinical trials, and the parallel review program with concurrent review by CMS and FDA.

The latest pathway is the breakthrough designation pathways that provide coverage for 4 years. After 4 years, CMS proposes that the product should have a national coverage decision that is either affirmative, restrictive, denied, or coverage through an LCD.

During the open public comment period, closing on 2 November, CMS submitted questions to stakeholders: Should CMS open a national coverage analysis if an application is not issued an LCD within 6 months of the pathway expiration period? After 4 years, should CMS make a decision about coverage? In addition to devices, should the pathway include diagnostics and biologics? Should CMS require or incentivize manufacturers to submit outcomes data or enter a clinical study? Should CMS require manufacturers to opt in or opt out of the pathway, given that it is now voluntary? Should manufacturers affirmatively opt in or opt out? Should off-label use be covered and under what circumstances?

The second part of the rule is about codifying reasonable and necessary. CMS has not codified this concept clearly, and MACs make a determination on a claim-by-claim basis. There are three criteria for a device to be reasonable and necessary. First, a product must be safe and effective; second, a product must not be experimental or investigational; and third, the product must have an appropriate duration and frequency. To meet the third criterion, the item or service must either 1) adhere to best medical practice and standards, be delivered by qualified health care personnel in a qualified health care setting, and be as beneficial as a medically approved alternative, or 2) be covered by commercial insurance plans except where evidence indicates that there are clinically relevant differences between Medicare beneficiaries and commercially insured individuals. CMS recognizes the need to provide a clear definition of reasonable and necessary so that innovators can better predict coverage.

.

How Medical Specialty Societies Influence Reimbursement

Mark Carol | Focused Ultrasound Foundation

Mark Carol updated participants about the coding process used in reimbursement for procedures. To be used clinically, every procedure must have a specific reimbursement code and payment associated with that code. A code consists of a C-code granted by CMS and a Current Procedural Terminology (CPT) code granted by the American Medical Association (AMA). Payment is assigned by CMS or the AMA based on real-world usage and cost data derived from hospitals. Professional societies play an important role in the issuance of a CPT code by the AMA, and published guidelines are used by most payers to make coverage determinations.

The AMA looks to professional societies' guidelines for support and issuance of a code and CMS uses best available clinical information to support need for a code. Coverage is at the discretion of each payer and variations in coverage exist within the different regional players (there are 12 MACs and 36 independent and locally operated Blue Cross Blue Shield [BCBS] companies). A specific service is covered only when determined by the payer as *reasonable and medically necessary* to prevent, diagnose, or treat illness, disease, an injury, or a condition. Insurers have no contractual obligations to reimburse a procedure that has not been shown to confer clinical benefit.

Evidence-based coverage policy rests on a comprehensive assessment of the evidence of effectiveness of a procedure in clinical use. Most professional societies have issued clinical guidelines using this evidence-based approach. Guidelines require 1a level of evidence obtained from systematic reviews or randomized clinical trials (RCTs). Evidence level 1b is derived from an individualized randomized clinical trial. If neither evidence is available, a society may rely on expert opinion. Inclusion of a procedure in a guideline does not guarantee coverage by a payer, however; the lack of inclusion in a published guideline is reason for the insurer to deny coverage. For example, CMS officially recognizes the National Comprehensive Cancer Network's *NCCN Drugs & Biologics Compendium* as a mandate to establish coverage policy and coverage decisions for these medications in cancer care. Similar requirements are expected in coverage decisions for devices.

Commercial payers conduct extensive literature research through their respective internal medical review teams and committees. Central to their evaluations are professional and specialty society opinions and treatment guidelines.

Coverage decision process for payers

Mark Carol presented two examples of coverage decisions made by payers for two devices. The application of HIFU in primary prostate cancer consists of a transrectal outpatient procedure that has been used to treat 80,000 men worldwide and is commercialized in the US. This procedure provides equivalent or better disease control than radical prostatectomy and is superior to surveillance. The side effect profile is also improved, with

significantly lower incontinence levels and preserved erectile function compared with radical prostatectomy. HIFU is preferred for localized treatment of cancer. Guidelines by the American Urological Association determined that these interventions are not standard of care due to the lack of comparative outcome evidence (no 1a or 1b level of evidence) that HIFU was equivalent to radical prostatectomy. There were no RCTs of HIFU for treatment of prostate cancer. The National Cancer Institute and most physicians did not consider HIFU as first-line treatment in prostate cancer. Referencing professional society guidelines, commercial payers, including BCBS, CIGNA, and Aetna deemed HIFU in prostate cancer as not medically necessary, investigational, or experimental, and lacking clinical evidence, and issued a negative coverage determination.

In contrast, in the second case, HIFU ablation in advanced stage prostate cancer is recommended by the NCCN, in addition to cryotherapy or brachytherapy for recurrent prostate cancer without metastases after treatment with radiation therapy. Consequently; Cigna, Aetna, and several MACs determined that HIFU is medically necessary as localized treatment for recurrent prostate cancer. CMS also determined that HIFU was considered medically necessary for recurrent prostate cancer based on NCCN guidelines.

Coding and coverage are critical to the success of new technology. Organizations developing a new technology must determine whether it will meet the criteria for coverage with these codes. Professional societies have significant influence on the issuance of a CPT code. It is important that device companies reach out to professional disease societies' committees and discuss clinical evidence. These societies are the determining factors in code coverage decisions through the guidelines they issue. A strategy needs to be in place to provide the level of evidence necessary to include the device in the clinical guidelines.

• • • • •

Real-World Examples of FUS Site Success

Panel

MODERATOR

Mark Carol | Focused Ultrasound Foundation

PANELISTS

Roberto Blanco Sequeiros | University of Turku, Turku HIFU Research Centre

Matthias Matzko | Helios Amper Klinikum Dachau

Sepehr Sani | Rush University Medical Center

Stephen Scionti | Scionti Prostate Center

Building a successful FUS practice is a complex process that requires knowledge of regulatory and reimbursement limitations that determine how to best use the technology. It requires the ability to navigate the political climate within a hospital or practice to enable the integration of a new technology. The panel of FUS surgeons will share their stories about building their FUS practice.

How to setup a center for HIFU, Finland

Dr. Blanco Sequeiros reviewed the prerequisites for a successful setup, namely, having a clinical need for HIFU and knowing the projected number of patients for HIFU. In addition, the practice should recruit principal investigators and doctoral students to prepare clinical and research applications for independent review boards. Factors that helped the success of his HIFU practice included a long history in performing MRI, staff enthusiasm to expand and adapt image-guided therapy (IGT) in HIFU, and strong vendor commitment during the HIFU installation. The multidisciplinary team included a urologist, anesthesiologist, radiologist, techs, and other health care professionals who worked in close collaboration.

Dr. Sani described successes in developing his HIFU practice program. The center was at a private hospital affiliated with an academic medical center, yet operated similarly to a community center. The hospital was in Chicago, a large metropolitan area with a high population density, including a large tremor patient population. The team researched referral sources and initiated conversations with them. Neurologists delivered repeated education sessions to practicing physicians at the hospital through grand rounds and online symposia. Primary care providers (PCPs) and general neurologists were contacted. The team built a large database of potential patients and referring providers. The program had a strong online presence with content that met the needs of the patient population. Clinical outcomes data were provided to referral sources and helped build trust in the provider community. The program included a neurosurgeon and a neurologist working closely to evaluate patient eligibility, a patient coordinator, a skilled MRI technologist, an advanced practice health care provider such as a physician assistant, and clinician nurse providers (registered nurse [RN], advanced practice nurse [APN]). Essential components included developing a personal relationship with patients, establishing a strong relationship with referral sources, and working through a dedicated patient coordinator.

Building an FUS practice

Dr. Scionti described building his private practice. The practice has a strong belief that FUS can provide effective approaches to prostate cancer treatment while maintaining patient quality of life (QOL). The technology provides image-based diagnoses and alternatives to standard surgery and radiation therapy approaches. Dr. Scionti built his radiology skills through partnership with a skilled radiologist in prostate MRI, reviewing patient cases, and understanding lesions. The practice worked closely with billing personnel at the hospitals to better understand reimbursement for this service. These efforts helped reduce out-of-pocket costs for patients and prevented barriers to access. A total of 750 patients have received HIFU since 2015. Building a successful HIFU practice starts with the core belief that this technology affords patients a good balance between treatment and QoL. It is important to develop the skill sets, master the platform and the image-guided ablation software, establish a good relationship with a radiologist, and communicate with hospitals about reimbursement. Above all, it was the passion to bring this technology to patients that built this large successful US practice.

Dr. Matzko told his story of building the FUS center in the Munich area within a 450-bed hospital. The FUS center, specializing in uterine fibroids, opened in 2008 as the third center in Germany and it is the only one remaining. It is most important to understand the needs of the patient, offer other treatment possibilities such as uterine embolization as well as the entire surgery spectrum, and give patients a treatment recommendation. Good clinical results strengthen relationships with gynecologists and help referrals. Careful patient selection is essential to delivering a consistent high-quality therapy that will lead to daily referrals. A full-time patient manager was hired, services were marketed online, and the team delivered presentations to referring doctors and gynecologists. The clinic expanded its patient services with time, increased MRI imaging capabilities, and performed more patient evaluations to assess FUS eligibility versus different treatments. For instance, as many as 70%–75% of patients were not FUS eligible.

As such, the clinic established strong relationships with patients. There was a strong collaboration with gynecologist partners for referrals. Patients came from Germany, other European countries, and from all over the world. Online presence was very important: 90% of patients contacted us through the internet. Treatment success attracts media attention, but more importantly, it justified reimbursement from insurance companies. Ours was the only center that offered insurance coverage for FUS for uterine fibroids.

The panel discussed the importance of collaboration, referrals, and other considerations in building an FUS practice.

1 Question to Dr. Matzko

How important is collaborative work and referrals from outside the community as opposed to from within the hospital?

It depends on the ultrasound application. In uterine fibroids, collaboration with gynecologists is important for the long term. Having robust referrals from outside the hospital is as important as internal referrals to build a large-volume program for the long term. More than half the referrals are from outside our center in Germany, and we perform patient selection.

2 Questions to all

In prostate cancer, do you expect to see younger patients requesting FUS for low-grade disease instead of active surveillance? What about intracranial and gynecological applications of the technology?

Dr. Scionti: Yes. This ultrasound technology preserves vital organ structures and functionality as opposed to radical therapy or surveillance. Ultrasound in prostate cancer treats low-grade local tumors.

Dr. Matzko: In uterine fibroids, FUS is a minimal or non-invasive technique and is anatomy sparing. That is the main reason why FUS is the treatment of choice in benign disease in uterine fibroids.

Dr. Sani: In movement disorders and tremor applications, ultrasound improves dramatically the QoL rather than being a cancer treatment. There is a large population with movement disorders, and patients with very severe symptoms who refuse invasive treatment may elect these technologies. QoL is paramount to these technologies in the tremor application.

3 Question to all

How do you apply the relationship with colleagues in the intracranial setting?

Dr. Sani: Getting buy-in from colleagues was essential. In this MRI-mediated modality, planning the right acquisition and maintenance was important and required close collaboration with colleagues and administration. The relationships we developed continue to benefit both radiology and neurosurgery disciplines.

Dr. Matzko: In the uterine fibroid application, as a radiologist, it was important to get input from the gynecology department. It was a close collaboration where both physicians studied cases together and the practice gained knowledge in gynecology from a radiological standpoint in treating fibroids. With time, the radiologist becomes less dependent on collaboration.

4 Question to all

How does the uptake of FUS at your practice impact treatment at competitor practices?

Dr. Scionti: The FUS patient population in prostate cancer is different from patients who receive standard therapies. Therefore, we do not pose a threat to our colleagues in radiation oncology. This is a patient-driven treatment where patients hope to be candidates for treatment. Most patients are from out of state and are seeking alternatives.

Dr. Sani: In the setting of intracranial movement disorders, tremors, and deep branch stimulation, patients are very well educated and connected with information. More than half of the patients are not local and are seeking an alternative. We are the largest established clinic for movement disorders, and the facility benefited from the technology.

Dr. Matzko: The hospital was the first to offer this technology and has since maximized MRI utilization and incorporated infusion biopsies. The practice raised awareness about this approach, which has resulted in increased service offerings. Similarly, the practice in Germany acquired an extra MRI just for FUS, and it is fully booked until next February. Additional MRIs are planned to check patient eligibility.

Dr. Sani: It might be difficult to measure downstream of new technologies through one institution in a Chicago hospital. In the movement disorders, tremor modality, FUS treatment causes dramatic improvement of outcomes, and patients are very happy. Providing good outcomes gives a first exposure to the inpatient facility. It has also given us substantial exposure in the surrounding centers and states.

5 Question to Dr. Sani

How difficult was it to get approval from the facility, academic center, or community hospital? Such practices challenge normal referral patterns and may be perceived as competitive with existing technologies.

It was more labor intensive than difficult. To obtain administrative buy-in, the practice should have a solid business model that shows revenue. Our approach was collaboration with neurologists and radiologists. We conducted several conversations and persisted through explaining the joint benefit to both our disciplines.

6 Question to Dr. Matzko

What has been the main obstacle in creating the FUS program?

The lack of reimbursement during the initial phase. In Germany, the social security system reimburses all health care costs and it was difficult to convince patients to pay out of pocket for this procedure. After 1.5 years, the insurance companies were onboard. In a university setting, it was bringing everyone to the table. Showing that this technology is revenue positive to the administration necessitated several meetings. Reimbursement is a very important piece. Ultrasound practices do not appear in clinical guidelines, and further research is warranted.

.

Training Certification and Credentialing

Panel

MODERATOR

Mark Carol | Focused Ultrasound Foundation

PANELISTS

Mathieu Burtnyk | Profound Medical

Karen Cornett | SonaCare Medical, LLC

Hugo Embert | EDAP Technomed Inc.

Amit Sokolov | Insightec

Mark Carol introduced the panel and highlighted the importance of certification and credentialing. Certification is the process of providing someone with an official document attesting to a status or level of achievement and is provided by the manufacturers of a device. Credentialing is the process of establishing the qualifications of licensed medical professionals and assessing their background and legitimacy. Credentials are issued by the facility where the technology will be performed. In this series of presentations, professionals at their respective institutions will share processes and requirements in the form of training programs to educate clinicians and support staff on the use of new technologies.

Hugo Embert presented on training programs at his company. EDAP companies are manufacturers and distributors of HIFU devices, approved in the US for the ablation of prostate tissue and in other parts of the world for the treatment of prostate cancer. For the Focal One device, the company developed a complete training program and delivered the Focal One user license certification. This program is divided into three phases: first is a general introduction to HIFU and its applications in prostate treatment, second is hands-on practice of the procedure on patients, and third is completion of the certification.

Phase 1 includes theory and case observation and can be completed in person. The trainee travels to meet the expert scientist. It is the preferred method as it allows peer-to-peer interaction between neurologists. During the COVID-19 pandemic, phase 1 case observations were conducted online where trainees could see the operating room (OR) in real time and interact with experts during the procedure. By the end of this phase, trainees could discuss the HIFU procedure with patients and start scheduling them. Phase 2, key to the training, consists of training by a proctor (a urologist who has performed 30 procedures or more and is certified as a proctor) sent to the trainee's OR and who will treat patients. Phase 3 consists of application support of the physician and staff. An EDAP-certified application specialist will work with OR staff to set up the device and train them on probe disinfection and handling, patient installation, and clinical application. The application specialist will assist the urologist in operating the device during the procedure. This phase continues for 5 to 10 patient cases. After phase 3, the trained urologist can get a user license. The EDAP-application specialist revisits the site after 6 months to make sure the urologist is comfortable and clinical results are showing.

Karen Cornett described the SonaCare Medical program, which includes online training, simulator sessions, in person proctoring, as well as online remote case support. Users have access to libraries, key opinion leaders' experiences with Sonablate HIFU, live case observations, free exchanges between proctor and trainee, refresher simulator sessions, and patient outcome analysis post-HIFU procedure. The physician is scheduled for simulation sessions with one of the SonaCare team who has control of the software ablation techniques. Upon completion of a pre-case training pack, a technical proctor joins for the first five cases. SonaCare offers online remote support during the procedure, allowing the physician to interact with the proctor as needed, a feature highly appreciated by physicians. SonaCare Medical offers educational opportunities, covers advanced HIFU techniques, and allows collaborative discussions. The technique is easy to use and offers resources to experienced users.

Amit Sokolov discussed Insightec, which owns MRI FUS products that are approved in the US for movement disorders, uterine fibroids, and pain palliation for bone metastases. The company training program is regulatory approved and is delivered on-site by application specialists. The training program prerequisites are the clinical skills required to safely and effectively treat patients with Exablate, certification in the use of MR scanners, assessment of MR images, and patient management in the applicable medical field.

The first part of the training is in the classroom and is theoretical (operation, safety and labeling, inclusion and exclusion criteria, system operation and simulation) as well as hands-on using phantoms (operation for treatment simulation), a dry run of the procedure, and education about treatment planning. The proctoring sessions cover the entire procedure from patient preparation through treatment stages and post-treatment imaging. The team is evaluated with a grading of 12 tasks, each graded from 1 to 5 on the ability of the team to perform the procedure independently. With COVID-19, the program was modified to require additional prerequisites and to add a remote connection to the system workstation. Education and communication were through calls and cameras.

Mathieu Burtnyk spoke about Profound Medical's TULSA-PRO, an MRI-guided transurethral ultrasound ablation device, and the training program. New ultrasound technologies require complex, disruptive procedures that challenge existing models of care delivery and require new physician collaborations, such as urologists interacting within an MRI environment and working with support staff. The Profound Genius Services program creates scientific teams committed to establishing successful TULSA practices.

In the first part of the training, expert users learned theory and advanced analytics to find specific bottlenecks that can be improved. Second, the program forms close relationships with physicians and reviews patient eligibility for TULSA treatment. Efficiency targets are set: The proposed workflow allows a 2-hour window per procedure and treating four patients per day. In addition, the program aims to have a holistic view of each site, including patient processing within the practice, transitioning from one patient to the next, and handling patient anesthesia that is required with MRI. In summary, the three core areas of the Genius Services program include patient eligibility reviewed by multidisciplinary team members; staff training, including physician and MRI technologist, on product use; and optimization of the workflow using data analytics.

FDA regulations require manufacturers to train users on safe and effective use of their products. Manufacturers do not consult on physicians' practice of medicine in the context of these technologies. Credentialing needs to be further developed. There is a need for a professional society to provide credentialing for users in the field as the technology expands, to provide training on MRI and ultrasound basics and medical considerations applicable to the whole field.

1 Question to all

How do certification programs vary from one country to the other, especially for manufacturers who have installations in Asia?

Panelists agreed that the basics remain the same and adjustments are made in regulatory applications. The content is translated in local languages and the training is delivered by local application specialists familiar with the local hospital culture. The certification process and grading forms are the same worldwide. In general, installation was more challenging due to COVID. Proctors cannot fly in and there is a lack of locally available proctors, so manufacturers adapted with newer tools and techniques.

2 Questions to Dr. Burtnyk

As a relatively new entrant at the time of COVID-19, has Profound Inc. had issues with transporting their model to other regions of the world?

What can we learn from COVID in terms of adjustments that might benefit credentialing and certification programs as we move to the post-COVID era?

Profound aims to standardize training and boarding process across all sites internationally. There were challenges in the US during commercialization. We respect language differences in each country. The pandemic introduced remote support and allowed us to grow and be successful. This approach helped us standardize programs internationally because we did not have local proctors.

There were delays with proctors having to quarantine in the host country and upon their return home. Sonalink enabled remote training with physicians and staff members, service setup, and performance through remote access. It was a success that will continue to be used.

The skills learned to provide online education, remote access, and observation tools will be beneficial in the future. It is harder to get connected and deliver remote access in larger institutions due to firewalls and other regulatory concerns.

It is a time-consuming and challenging process to connect remotely to different sites in different countries. Many of our customers cannot be reached remotely, especially in China.

3 Question to Dr. Burtnyk

As a company that applied its approach during COVID times versus others who adapted their programs, how did COVID impact the thought processes at Profound Inc.?

At Profound, the concept of remote support was on the forefront of our market strategy. It is very challenging to enable connections with regulations in place. Recognizing these steps initially in the design and project plan helps in risk mitigation in the future. Interpersonal relationships are affected, including physician-to-physician case observation and physical

presence in the MRI suites. It is important to note that virtual connection has a lot of advantages, for example, it allows additional expert eyes that may not interfere, or in cases where MRI rooms are very small, it accommodates needed staff.

4 Question to all

Have the hospitals developed any common credentialing criteria, or has there been standardization across hospitals or institutions? The FUSF is aiming to develop national or international standards for credentialing specific to organ systems and treatment, and a training program for physicians and surgeons on the use of ultrasound.

Panelists agreed there should be a common training course for all physicians to learn the basics of ultrasound and the physics of ultrasound for uterine fibroids, prostate ablation, and other applications. For instance, some users in Europe have started to develop fellowships about minimally invasive prostate therapy emphasizing HIFU. Their program used some manufacturer materials and adds medical and clinical components, which are not covered by the companies.

There is a lot of variability especially in the academic institutions. There are differences in credentialing requirements. However, all hospitals required, at a minimum, that physicians complete the manufacturer training program.

Credentialing is decided by hospitals that set criteria to accept a service (i.e., a minimum of 10 cases, required monitoring internally or externally, only physicians previously trained to perform first few cases).

Panelists were in favor of FUSF developing a basic training program for ultrasound and handling the certification and credentialing process.

• • • • •

Track B

.....

Brain Technical—Imagining

Oral Presentation Q&A

Presentations highlighted the use of magnetic resonance (MR)-guided FUS (MRgFUS) in the brain.

MODERATORS

Meaghan O'Reilly | Sunnybrook Health Sciences Centre

Viola Rieke | University of Utah

SPEAKERS

Steve Leung | Stanford University

Comparison of transcranial focused ultrasound treatment planning using MR and CT images

Sumeeth Jonathan | Vanderbilt University

Rapid autofocusing of MR-guided focused ultrasound acoustic pressure fields using MR-ARFI with spatially coded emissions

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

Using phase data from MR temperature imaging to visualize anatomy during MRI-guided focused ultrasound neurosurgery

MRI-based thermal dosimetry during focused ultrasound thalamotomy

Xinqiang Yan | Vanderbilt University Medical Center

"Propeller beanie" passive antennas to alleviate dark bands in transcranial MR-guided focused ultrasound

1 Questions to Dr. Leung

In the study of transcranial FUS using MR and computed tomography (CT) images, are the MR-simulated CT images able to pick up intracranial calcifications during thermal FUS treatments?

These were not identified in the ex vivo human skulls used in the experiment; in vivo experiments are needed.

If the images are taken with the transducer in place, do you think the image quality from the current system with body coil imaging would ever be sufficient enough to get this kind of image quality using MR?

The MR artifact caused by the head transducer could be a problem. Any approach to minimize it, such as the propeller beanie, would be really great.

Did you compare the thickness of cortical and trabecular bone?

This was not examined.

2 Questions to Dr. Jonathan

In the study on rapid autofocusing using MR-acoustic radiation force imaging (MR-ARFI), the approach seems to work well with the basic aberrator, but there were only four logical

elements in that aberrator. How does that scale to a more complex aberrator? And is there a hit on the time it takes to do the correction?

In a realistic system, logical elements can range from a few hundred to a few thousand. The system used in this study has 128 elements and scaling up could be done within a realistic time frame. Recent work with MR-ARFI used groupings of elements. In this study, a small number of logical elements worked well. Simulations have been successful with up to 120 elements.

Would you need to repeat the MR-ARFI each time you scan within the brain?

Yes, but it would likely require a reduced number of acquisitions.

The transducer that was used was only about 10 cm and the images had a 5 cm x 5 cm field of view. Would there be any issues with scaling up to some of the large brain systems that are used clinically?

This should not cause any sort of intrinsic limitations in how the technique would be implemented. The size of the field should not be a limitation. It will depend on resolving differences in the contributions at the amplitude and phase from all the different elements. It really comes down to the signal-to-noise ratio (SNR) of the acquisition.

3 Questions to Dr. McDannold

In the study on MRI-based thermal dosimetry, what factors might affect your estimates of 17 CEM43 (cumulative min at 43°C), which is lower than that seen in reports by Seasons and Jones?

Seasons compared the dose to the lesion and T1-weighted images, and this appears to be smaller than the T2-weighted images used in this study. Even a small difference in methodology could give a wide shift in the apparent dose.

The contours between the thermal dose and the actual lesion volume matched very well.

Some assumptions were needed about how the shape would be retained when steering the beam into different locations, but it seemed to work well on average.

In the study using phase data to get anatomical information, are you using all phase maps during heating or both before and after heating? How are you determining weights for weighted averaging?

All phase maps were averaged to get improved SNR from the individual phase maps. A weighted average of the different echoes was based on the SNR.

4 Question to all

For all of these studies, when might we see some of these techniques adopted in a clinical setting?

Dr. Leung: It will be necessary to first get the acquisition times down and then perform in vivo experiments in large animal studies.

Dr. Jonathan: MR-ARFI is a very promising technique and feasible in nonhuman primates. The limitation is in seeing it implemented on the InSightec system in clinical settings before translating it further.

Dr. McDannold: For phase imaging, it would be easy for the manufacturer to add a button for reprocessing the images, but a company may not want to for liability reasons. There will eventually be three-dimensional (3D) thermometry, but the values used now are working.

• • • • •

Brain Technical—Imaging

Panel

In brief presentations before the open discussion, two panelists discussed the challenges and recent developments in the use of MRgFUS of the brain. Dennis Parker reviewed the main challenges with its use, which are mainly focusing the ultrasound beam consistently through the skull and monitoring heating from the full beam (throughout the brain). Craig Meyer reviewed recent developments, highlighting hot spot thermometry, monitoring of skull heating, treatment monitoring with diffusion, and suppression of the water bath signal.

MODERATOR

John Snell | Focused Ultrasound Foundation

PANELISTS

Dennis Parker | University of Utah

MRI guided transcranial focused ultrasound of the brain

Craig Meyer | University of Virginia

Hot spot thermometry

William Grissom | Vanderbilt University

1 Question to all

When we met several years ago, ultrasound for treatment of central tremor was a new thing. How may some of those earlier issues have plotted a path to where we are today with MR-imaging research and transcranial FUS?

Dr. Parker: The two main challenges then were trying to measure temperature in three dimensions, which was being done primarily in nonbrain applications, and dealing with noise and artifacts associated with the water signal.

Dr. Grissom: Much time was spent discussing the chemical shift artifact seen in the temperature maps while heating. The hot spot kept blurring itself further and further. An idea that floated at the earlier meeting was multiecho thermometry. GE released a multiphase type sequencer to work with multiecho, which is basically the standard thermometry method.

Dr. Meyer: The water bath was a problem for doing a standard pre-scan, which was not reliable. We have since figured out how to do those pre-scans.

2 Question to all

Would the flow of water doped with iron cause phase artifacts in the brain?

Dr. Meyer: Some groups have been working with doping the water bath to get rid of the MRI signal, although the water flow is often turned off anyway during the procedure. The doping will likely not cause a lot of artifact because there is not much signal from it at the concentrations used. The main concern is cavitation in the water bath.

3 Question to all

Where do you think we are with 3D thermometry?

Dr. Grissom: Whole-brain thermometry will probably require some new hardware capabilities and coil technology. Segmented echo-planar imaging (EPI) has been a workhorse because it was easiest to implement but needs improvement. Some radial and spiral techniques are being studied. The combination of fast ways to acquire the data and accelerate image reconstruction should work but needs to be proven. There are much preclinical data, but methods need to be refined for clinical testing.

4 Question to all

At the moment we are constrained to either the body coil or, as it becomes available, maybe a two-channel receiver or a coil that would be a little closer to the head. What are your hopes and dreams for having a head coil for this technology?

Dr. Grissom: A “coil statement of need” has been generated, indicating exactly what researchers would like to see and the expected impact that any new coil developments would have on the field. Having adequate coil capabilities would allow for whole-brain thermometry and make off-center targeting safer. The challenges are that the coil should not interfere with the FUS beam or water circulation and should be usable with or without the water bath with similar levels of performance.

Dr. Meyer: Progress has been made and some two-channel coils are now available in other countries. However, multiple channels are needed to do advanced imaging. It is also not just the receiver coil but the transmitter that is important.

Dr. Grissom: Placing some kind of metallic structure above the head, such as high-gauge wire structures that minimally interfere with ultrasound propagation, can control and tailor the reflection of the radio frequency (RF) waves that come in from the bottom of the transducer. A configuration using two wires placed in a propeller-beanie configuration on the head is looking promising in an in vivo study, with improvements in the B1 fields measured with a D1 mapping sequence.

5 Question to all

While talking about blood-brain barrier (BBB) opening and drug delivery, and maybe histotripsy and neuromodulation, what is your vision for future research and MRI's role?

Dr. Grissom: We are starting to build lists of how to establish a coordinate system in the scanner to do accurate targeting outside the scanner using optical tracking and other concepts. For treating neuropathic pain, for example, we may want the patient to be in the scanner for one or two procedures, but not every treatment.

Dr. Meyer: This is an area of interest in non-FUS as well. Also, with the coil and B1 improvements, more can be done within the scanner at procedure time.

6 Question to all

Is there a role for functional MRI (fMRI) in transcranial FUS?

Dr. Parker: Yes. The problem with getting fMRI to work in the system is the challenge of SNR. There is a good chance that smaller transducers for the BBB opening and lower water volumes are coming and will be consistent with building a good coil.

.

Brain Technical—Miscellaneous

Oral Presentation Q&A

Presentations highlighted FUS applications such as histotripsy, high-intensity focused ultrasound (HIFU), and the remote use of magnetic resonance (MR)-guided FUS (MRgFUS).

MODERATORS

Meaghan O'Reilly | Sunnybrook Health Sciences Centre

Viola Rieke, University of Utah

SPEAKERS

Thomas Bancel | Physics for Medicine Paris – ESPCI

Computationally efficient transcranial ultrasonic focusing: Taking advantage of the high correlation length of the human skull

Comparing ray-tracing algorithm and finite differences modelling on a clinical device for HIFU brain therapy using the transfer matrix formalism

Daria Chupova | Lomonosov Moscow State University

Aberration correction for the transskull focusing of high-intensity ultrasound at various depths in brain

Rezida Galimova | Intelligent Neurosurgery Clinic

First in history remote start of MRgFUS treatment procedures due to COVID-19 epidemic

Zhongtao Hu | Washington University in St. Louis

Three-dimensional transcranial cavitation localization by four sensors

Ning Lu | University of Michigan

Transcranial MR-guided histotripsy treatment: An in-vivo pig study

Jonathan Sukovich | University of Michigan

Transmit-receive capable histotripsy transducer systems for real-time treatment localization and mapping and evaluating induced tissue damage

1 Questions to Dr. Galimova

When treating patients remotely with MRgFUS, what was the hardest part about the remote interaction? And how many cases have you done remotely?

This work was carried out at the first and only MRgFUS treatment center in Russia to help patients with movement disorders and was done remotely because of the COVID-19 pandemic. The most difficult part was selecting patients and doing everything step-by-step. The first operation lasted about 24 minutes; subsequent operations were about 10 minutes. When working together, it was like being in one room. The neurosurgeon realized that even very difficult neurosurgical procedures can be done using a digital approach with proper support, preparation, and teamwork. A total of 23 procedures have been completed to date.

2 Questions to Ms. Lu

In the study of transcranial MR-guided histotripsy, it looks like the acoustic window limits the number of transducer elements that can be used. What fraction was active for the histotripsy?

If the full hemisphere was fully populated, it would have 360 elements. To have an acoustic opening before treatment, only the bottom portion would have the space to pass the acoustic window. We only populated 120 elements at the bottom portion; all were actively used for treatment.

How long did the treatment take? And how was the MRI guidance done?

Treatment time was about 10 minutes, but the goal was not to optimize treatment time. Treatment time could be accelerated with a higher focal pressure. The time also depended on the volume; a larger target would take longer. Regarding MRI guidance, the sequence used was developed by Steve Allen and allows for monitoring cavitation events instead of thermal effects. Guidance was used to monitor pre- and post-treatment histotripsy changes and check for any excessive hemorrhage due to treatment.

3 Questions to Dr. Sukovich

In the study of transmit-receive capable histotripsy transducer systems, can you do phase and amplitude correction on the received signals and if so, are you planning to implement that?

Yes, phase and amplitude correction based on the acoustic cavitation emission (ACE) signals can be done but with a caveat. If the acoustic properties of the skull are not known, the correction of the aberrations, based on the signals, is done to the location of the bubble and not necessarily to the intended target position. It does not realign the position of the focus to where it should be if it is not where intended. On transmit, the aberration correction was done just to ensure getting a bubble to generate the ACE signals needed.

Could you use those same correction values on the receive side without considering using the ACE signals to calculate the corrections?

Yes, definitely. When done, it gives a fairly decent increase in accuracy on the localization results—about 15% to 30% when correcting the phase aberrations on the image reconstruction.

Have you planned or started any in vivo studies to look at these signals?

Not yet. There are receive capabilities on some other transducers currently used in rodent studies, but not yet through the skull. Some cadaveric work in a human model is planned.

.

Brain Technical—Beyond Ablation

Panel

MODERATOR

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

PANELISTS

Zhen Xu | University of Michigan

Histotripsy for brain applications

Lennart Verhagen | Radboud University

Low intensity focused ultrasound for neuromodulation

Jean-Francois Aubry | Physics for Medicine Paris

Different approaches to modulate brain activity with focused ultrasound

Elisa Konofagou | Columbia University

Brain modulation and drug delivery with FUS

In brief presentations before the open discussion, the panelists highlighted potential uses of FUS beyond ablation.

Zhen Xu discussed the use of transcranial histotripsy for brain applications. Potential advantages include the ability to reach a wide range of treatment locations and create a large treatment volume, without overheating the skull.

Lennart Verhagen discussed the use of low-intensity FUS for neuromodulation in primates and its clinical potential for treating brain disorders. Opportunities exist for developing long-lasting noninvasive modulation as a novel targeted treatment option in human neurology and psychiatry.

Jean-Francois Aubry discussed the modulation of brain activity by direct ultrasonic neuromodulation and opening of the blood–brain barrier (BBB) plus injection of a neuroactive agent. He reviewed studies in nonhuman primates and noted that the choice of neuromodulation device depends on the model and the target.

Elisa Konofagou reviewed current work on brain modulation and drug delivery with FUS. Opening of the BBB with FUS has improved motor and cognitive performance in nonhuman primates and has facilitated delivery of proteins, genes, and chemotherapeutics in mouse models.

1 Questions to Dr. Xu

When using transcranial histotripsy, how large could you make an area if you wanted to defocus the spot and treat a larger volume with one sonication?

Defocusing would reduce accuracy. It would be preferable to not defocus the spot but to use either electrical focal steering or mechanically move the focus to include a larger volume. Electrical focus steering alone allows for treating an area of 5 cm in diameter; mechanical movement can be used to treat a larger volume. Other considerations are treatment time needed and the biological response, i.e., how the body would react to acellular debris in the brain.

When thinking about treating tumors, how close could you get to the skull, both on the outer part and deeply?

In the treatment study, the closest so far was 5 mm from the skull surface. At that point, the limitation is not actually heating but prefocal cavitation.

Have you thought about purposely inducing bleeding or targeting an adjacent large blood vessel to assess potential risks?

The initial feasibility studies indicated a risk of bleeding if a vessel is hit at a high level of pressure, but there has been no evidence of excessive bleeding. In another study of the prostate in which heparin was administered before histotripsy, some coagulation effects were actually observed.

2 Questions to Dr. Verhagen

When discussing neuromodulation with FUS, you talked about modulating brain plasticity while not stimulating or blocking brain function. How do you think that works?

Brain stimulation using electromagnetic tools started out with simplified ideas of activating or inhibiting a region. Now, the area is more complex. In psychiatric disorders, in particular, a neural circuit can lock and have a hard time retraining or rehabilitating. Protocols using external stimulation to help boost downstream signaling cascades that lead to long-term potentiation and depression seem to be beneficial for allowing retraining and learning.

Do you think these effects may play a role in rehabilitation after stroke or brain injury?

Yes, a major role. Electromagnetic tools are being developed for compensation in various brain regions after stroke. It would be exciting to start using ultrasound to build on these foundations.

In a certain subset of patients, tremor returns several months after treatment. If that involves plasticity, do you think ultrasound could reduce it?

In protocols using transcranial alternating current stimulation to suppress the tremor, the circuit tries to escape the exogenous imposed oscillation, so the tremor keeps returning. Those protocols may be relevant for tremor in plasticity, where there is reorganization of the circuit over a longer time scale. Adaptive lower-intensity neuromodulation may be helpful when the tremor escapes ablation, for example.

Are there particular psychiatric disorders that might be more amenable to FUS treatment than others?

Most researchers are looking at circuits where treatments are known to work and trying to improve upon those. Many are considering obsessive-compulsive disorder, where the circuit is well-mapped and less complex than depression, which has enormous variation in patients.

3 Questions to Dr. Aubry

In the research on neuromodulation in alert nonhuman primates, one monkey seemed less responsive. What factors influenced susceptibility to neuromodulation with this technique?

The responses were related to the BBB opening and the delivery of gamma aminobutyric acid (GABA). In this study, the amount of GABA that actually entered the brain was not quantified, and more work is needed to reproduce these results.

What are the main safety concerns for neuromodulation and how would guidelines be established?

Safety guidelines and the need to set boundaries are being discussed. So far, low total energy has been used for acoustic neuromodulation and many reports confirm safety. However, consensus is needed to address both a mechanical index of peak pressure and a thermal index of maximum temperatures.

4 Questions to Dr. Konofagou

In the glioblastoma mouse model study, what was the temporal window of the FUS protocol?

The therapeutic agent was administered immediately after opening the BBB at a dose of 5 mg/kg.g

How did you control for the auditory artifact that can occur with neuromodulation, especially in small animals?

The study included groups with three different noise levels: an ambient group with only normal laboratory noise, a sham group with a speaker using a frequency and intensity similar to ultrasound, and a group with the actual FUS modulation.

• • • • •

Technology Research

Oral Presentation Q&A

Presentations highlighted investigations into new technological developments in the use of magnetic resonance (MR)-guided FUS (MRgFUS).

MODERATORS

Cyril Lafon | INSERM

Narendra Sanghvi | Focused Ultrasound Foundation, SonaCare Medical, LLC

SPEAKERS

Edwin Heijman | University Hospital of Cologne

Thermal dose performance temperature: A measure to evaluate MR-HIFU hyperthermia treatments

Vera Khokhlova | Lomonosov Moscow State University and University of Washington

A prototype system for boiling histotripsy in abdominal targets comprising a 256-element spiral array combined with a power-enhanced Verasonics engine

Kisoo Kim | University of California, San Francisco

Motion-robust, multi-slice, real-time MR PRFS thermometry for MR-guided ultrasound thermal therapy in abdominal organs

Xiaoyue Li | Columbia University

Harmonic motion imaging guided focused ultrasound (HMIgFUS) in an in vivo breast cancer mouse model for monitoring and assessment of lesion formation

Song Lin | The Hong Kong Polytechnic University

Gas-filled protein nanostructures as cavitation nuclei for molecule-specific sonodynamic therapy

Lifei Zhu | Washington University in Saint Louis

Magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU)-induced large-volume hyperthermia is feasible in deep and superficial targets in a porcine model

1 Questions to Dr. Heijman

Regarding the study on thermal dose performance temperature (TDPT), how does this metric correlate with a biological outcome?

This is just a first proposal with one treatment so far. Further study is needed about biological influences.

What is the benefit of this new metric compared to a conventional thermal dose?

TDPT gives more insights into the performance of the hyperthermia control algorithm, regardless of the set target temperature and treatment time. It is not only about the time but also the temperature level that is reached and continued over a longer time span. MR-guided FUS is used to achieve very accurate, even per pixel, temperature information.

2 Questions to Dr. Khokhlova

In the study on boiling histotripsy in abdominal targets, can the phase correction algorithm also detect obstacles and switch off some elements?

A specific experiment has not been done to address this but would be possible. The idea is to get a signal from the focus. If there is an obstacle in the way, there would be a shadow and less amplitude in the receiving elements.

How did you modify the Verasonics V1 system to meet your power requirements?

Very short pulses relative to high-intensity focused ultrasound (HIFU) treatments were used. The average acoustic power was within the limits of the system, but several additional capacitors were needed to maintain high peak power for a longer time. Some modifications were made to the software.

Why did your transducer design have that particular shape?

The spiral array was chosen because it was more compact and irregular and had a high filling factor.

You used Doppler for evaluating liquefaction. When the speed of 30 cm/sec was reached, did that indicate that tissues were liquefied?

The tissue was actually liquefied before that. With 10 pulses per point, the velocity went to 30 cm/sec. The velocity increases right after tissue is liquefied unless debris is present in the region.

3 Questions to Dr. Kim

In the study of proton resonance frequency shift (PRFS) thermometry for MR-guided FUS thermal therapy, how close are you to doing in vivo experiments?

One experiment was done using this approach in the liver of healthy volunteers. More reproducible experiments are needed with healthy volunteers.

In trying to find solutions for treating mobile organs, the prostate and spinal cord were used as examples. Do you think these targets move a lot?

For prostate, the motion is not like that in the liver or kidney, where abdominal organs can shift by the dilation of the lung.

What potential roadblocks do you foresee for clinical translation of the methods?

The goals are to make a transition to clinical hyperthermia therapy using MR-guided FUS with hyperthermia and develop a pipeline for measuring temperature in real time during free breathing. The limitations may be in cardiac motion, which can also lead to significant temperature errors. The algorithms need to be improved to correct for other kinds of motion in addition to respiratory.

4 Questions to Ms. Zhu

In the study of MR-guided HIFU in deep and superficial targets, do you want to do this for thermal ablation or to sensitize tumors before radiotherapy or chemotherapy?

The hyperthermia was designed to sensitize the tumors without damaging them. The tissue damage is also ideal and acceptable. In the future, the tissue damage within the heating area should be expected if the 58-mm diameter is used.

Can you describe the threshold planes used? And what acoustic power was used?

The Sonalleve® V2 system provided two planes for temperature measurement: a “near field” for monitoring tissue within the target area and a “far field” for measurements beyond the heating area. Two sites were chosen for tissue monitoring, and the two planes were used for limiting the temperature overshoot. The acoustic power used was 100 watts.

5 Question to Ms. Li

In the study of harmonic motion imaging and FUS, did you try averaging four times on the same frequency? Do you think this would improve your method?

Averaging across multiple frequencies was used because previous studies showed that using different amplitude-modulated (AM) frequencies was better able to increase the contrast of different tissue types. The AM frequencies were combined to combine the effects for different tissue types and stiffnesses. The same results would not be expected by just averaging the results from one single AM frequency.

.

Technology Gaps & Breakthroughs

Panel

MODERATOR

Cyril Lafon | INSERM

PANELISTS

Rajiv Chopra | University of Texas, Southwestern
MRI-controlled FUS using minimally-invasive devices

Kullervo Hynynen | Sunnybrook Health Sciences Centre
Transducer phased arrays, bubble mediated FUS applications, dose monitoring concepts for bubbles

Tatiana Khokhlova | University of Washington
Technology gaps and breakthroughs

Dennis Parker | University of Utah
Technology gaps in MRI guided focused ultrasound

Narendra Sanghvi | Focused Ultrasound Foundation, SonaCare Medical, LLC
Technology gaps and breakthroughs

The panelists gave brief presentations before the open discussion.

Kullervo Hynynen summarized technology gaps and breakthroughs related to transducer phased arrays, bubble-mediated FUS applications, and dose-monitoring concepts for bubbles.

Dennis Parker discussed technology gaps related to tissue treatment endpoint determination.

Narendra Sanghvi reviewed challenges and advantages of FUS-guided systems and cited HIFU treatment for early detected localized prostate cancer as a breakthrough.

Tatiana Khokhlova cited breakthroughs and challenges with histotripsy, FUS transducer design, and treatment simulation.

Rajiv Chopra discussed some strengths and weaknesses of MRI-controlled FUS using minimally invasive devices, and summarized challenges and opportunities.

After the presentations by the panelists, George Zhang from Shenzhen PRO HITU Medical Co. described the history, research, products, key technologies, and treatment sites of his company.

1 Questions to Dr. Hynynen

Can you explain more about the concept of bubble-mediated bioeffects, mentioned as a challenge for the future?

MRI has been used to monitor the effect of using bubbles, but it is not clear how the opening is happening and how to control it, and the impacts of the bubbles in the tissue. Certain things can be demonstrated in animals, but controlling and measuring the exposure in patients is not known. The biological responses might be different for different indications.

Can you give an example of metrics for the blood-brain barrier (BBB) opening?

Permeability can be increased to a degree, but it is not highly controllable yet. There is a huge opportunity for looking at different kinds of bubbles and using them to stimulate different kinds of effects in the brain.

Has anyone explored using positron emission tomography (PET) or computed tomography (CT) instead of MRI to monitor the BBB opening? Is this feasible?

Some studies were done using PET imaging after using a tracer. It was useful to quantify the amount of molecules getting into the brain. Spatial resolution is not that high. For CT, ionizing radiation might be a problem.

2 Questions to Dr. Parker

What should be done to go further with MRI for thermometry or other applications for monitoring HIFU treatment?

For monitoring ablative procedures, the goal is to do very rapid three-dimensional temperature measurements. The hope is that the combination of T1 and the proton resonance frequency thermometry simultaneously would allow detection of tissue changes occurring dynamically. This would be a useful additive for ablative procedures. For other procedures for the BBB opening and neurostimulation that require nonthermal effects, it will be a challenge for MRI, so ultrasound-guided methods may have some advantages.

How far are we from performing temperature measurements in three dimensions in MRI?

At least three or four researchers are studying this and the methods are working well. The challenge is to use these methods dynamically in a commercial system. The goal is to get the companies that are doing thermal ablation to build a system and get it FDA-approved with one of the three dimensional techniques.

3 Question to Dr. Sanghvi

HIFU has been very efficient for treating prostate cancer. What is needed to replace conventional methods like robotic surgery or radiotherapy with HIFU?

The majority of clinicians know how to use ultrasound for diagnostic purposes but do not know how it works from a therapeutic aspect. Medical schools need to adapt so that the burden of teaching medical practitioners does not fall on the researchers. The devices need to be easy to use and adopt. Practitioners do not have time to understand the physics. Cost also plays a major role, so commercialization must parallel the research. Otherwise, the technology will remain in the laboratories.

4 Questions to Dr. Khokhlova

How is it possible to model treatment in real time and for what purpose?

The uncertainties in tissue properties do not necessarily lie with the changes in the tissues that occur with treatment but with the intervening tissues not meant for treatment such as bone or fat. Being able to accurately predict the acoustic field and temperature field before any changes occur is very important. If the procedure could be made patient-specific from a recent or real-time CT scan, that would be an enabling tool for doctors, especially if it was user friendly.

There are at least two types of histotripsy. Which would you favor, depending on the application?

They all offer their own benefits. For example, cavitation histotripsy or microtripsy, as it is currently primarily used, is probably the best bet for transcranial applications. For boiling histotripsy, the best niche is miniature or limited acoustic access applications such as transluminal or transabdominal, where acoustic access is a problem.

5 Question to Dr. Chopra

When working on the design of these devices, some have said that the same can be done with radio frequency (RF). Why should we continue to work on these devices?

High precision is possible with ultrasound, especially when coupled with good image guidance. For applications where accurate thermal dosimetry is necessary, there is no question that ultrasound will offer advantages. There are probably applications where a simple device with less overhead, like RF, is adequate. It just depends on the application. For the prostate, where millimeter precision is really important, there is no match for using FUS.

6 Question to all

What do you think will be the applications in the next 5 years that will lead to treatment of most patients?

Dr. Hynynen: The blood–brain barrier application is going to be very widely used for cancer patients first, and then in Alzheimer’s disease and Parkinson’s disease.

Dr. Khokhlova, Dr. Chopra, and Dr. Sanghvi: Prostate treatment is another obvious application for both benign prostatic hyperplasia and cancer, eliminating radiation and radical treatments. Hundreds of thousands of patients have already been treated.

Dr. Parker: Neurostimulation and immune response are also very intriguing.

• • • • •

Closing Remarks

Neal Kassel

Focused Ultrasound Foundation

“Wow, what an incredible, stunning experience,” began Dr. Kassel. The collective acceptance to bring the 2020 Focused Ultrasound Symposium to a new platform was nothing short of astounding. This year’s virtual meeting facilitated attendance, with 1,700 participants from 57 countries participating over an extended 5-day period. There were nine keynote and special lectures, more than 250 scientific presentations, 19 panels with 108 panelists, 31 roundtables, and seven fireside chats—all of which reflected tremendous growth in the field since the 2018 in-person event.

Dr. Kassel thanked the participants, sponsors, and foundation team for their patience, understanding, and contributions. He solicited feedback on how to improve the experience, which was not without its glitches. The purpose of this symposium is to share information and knowledge, foster collaborations that lead to partnerships and strategic relationships, and to have fun. We missed seeing one another in person. Progress and extensive research have translated to a superabundance of new clinical indications, clinical trials, regulatory approvals, reimbursement, manufacturers and investment in the manufacturing segment, number of treatment sites, and the number of patients treated. Evolution in fields like focused ultrasound occurs exponentially. We have passed the inflexion point in the field. The challenge is now to make “if and when” become “now.” Looking to the future, the next International Society for Therapeutic Ultrasound (ISTU) meeting is scheduled for June 6–9, 2021, with options to attend in person and virtually. The European meeting in Rome, Italy, will be in October 2021. The 8th International Symposium on Focused Ultrasound is scheduled for October 23–28, 2022, in Bethesda, Maryland, with in-person and virtual attendance options. The foundation will also sponsor a robust number of workshops in the next year. Dr. Kassel concluded with his signature closing, “Thank you. Stay safe, be well, and be happy.”

Presentation Take Home Messages

Symposium 2020 Scientific Program

Contents

148	Brain Tumors
149	Psychiatric Disorders
149	Neurodegenerative Disorders
150	Blood-Brain Barrier Opening and Drug Delivery
153	Neuromodulation
154	Epilepsy
154	Movement Disorders
154	Cancer Immunotherapy
156	Prostate
156	Breast Tumors
157	Liver, Pancreas, Kidney, Colorectal, Head & Neck Tumors
158	Musculoskeletal Disorders
159	Women's Health
159	Cardiovascular Disorders
160	Pediatric Indications
160	Veterinary Indications
160	Technical
166	Miscellaneous

Symposium 2020

Scientific Program Take-home Messages

7th International Symposium on Focused Ultrasound



The 7th International Symposium on Focused Ultrasound is the world's leading forum for sharing translational and clinical advances in focused ultrasound.

We asked each researcher who submitted an abstract to summarize his/her work in a brief sentence. Browse this list of “take-home messages” for an overview of the meeting's topics.

Please note that some items are duplicated if more than one category was applicable.

.

Brain Tumors

Zachary Englander | Columbia University

Focused ultrasound mediated blood-brain barrier opening is safe and feasible following radiotherapy in a murine diffuse intrinsic pontine glioma model.

Yutong Guo | Georgia Institute of Technology

Our integrated experimental and computational framework revealed that microbubble-enhanced FUS in combination with 40 nm cationic nanoparticles results in robust nucleic acid delivery in brain tumors.

Chulyong Kim | Georgia Institute of Technology

Ultrasonic thermal stress promotes acute changes in the transvascular transport dynamics in brain tumors and promotes the delivery of chemotherapy encapsulated in heat sensitive nanoparticles.

Benoit Larrat, PhD | Commissariat à l'Energie Atomique et aux Energies Alternatives

In a rat syngenic brain tumor model, FUS induced BBB opening significantly enhances delivery and efficacy of a cocktail composed of anti-PD1 antibody together with drugs limiting pro-tumoral inflammation.

Chia-Jung Lin | NaviFUS Co. LTD

Focused ultrasound combined with clinical microbubbles can raise cerebral oxygen content, which may also contribute to the effect of radiation therapy for brain tumor treatment.

Ying Meng, MD | Sunnybrook Research Institute

In this study, we will investigate the safety and feasibility of MRgFUS induced BBB opening for trastuzumab delivery for intracranial metastatic lesions in Her2-positive breast cancer patients.

Christopher Pacia | Washington University in St. Louis

FUS-liquid biopsy is a promising noninvasive tool for the diagnosis of brain tumors, providing valuable molecular and genetic

information. Optimization of FUS-LBx parameters, such as FUS pressure, microbubble dose, and blood collection time, will improve its efficacy and safety.

So Hee Park, PhD | Yonsei University College of Medicine

The survival rate up to 1 year was 100% in six patients who underwent BBBD for GBM. The median PFS in patients with recurrence was 13.5 months. None of the patients had immediate or delayed BBBD-related complications.

Chenguang Peng | Brigham and Women's Hospital

We tested phase change nanoemulsions for facilitating transcranial ablation of healthy and tumor tissues. The results suggest that nanoemulsion-mediated ablation can provide better spatial control of lesion formation and destroy a larger fraction of tumor compared to microbubble-mediated ablation.

Francesco Prada, MD | Fondazione IRCCS Istituto Neurologico

Sonodynamic therapy is feasible and safe. No damage occurred in the healthy brain when combining low-intensity ultrasound with sonosensitizers.

Richard Price, PhD | University of Virginia

Opening the blood-tumor barrier in intracranial melanoma with focused ultrasound (i) elicits transcripts associated with inflammation, (ii) increases antigen within the tumor, and (iii) contributes to dendritic cell maturation. Nonetheless, the response is mild and transient.

Richard Price, PhD | University of Virginia

Immuno-PET revealed that mCD47 timing relative to FUS blood brain/tumor disruption markedly impacts antibody penetrance in murine gliomas. A rational FUS-mediated mCD47 delivery paradigm leveraging these insights constrained glioma outgrowth and offered survival advantage.

Jason Sheehan, MD | University of Virginia

Sonodynamic therapy (SDT) coupling high frequency focused ultrasound and 5-ALA can induce apoptotic cell death in high grade glioma models. The system that we built will allow for additional testing of sonosensitizers and optimization of SDT parameters.

Tao Sun, PhD | Brigham and Women's Hospital, Harvard Medical School

Our results provide preclinical proof-of-principle for pairing FUS with PD-1 blockade therapy in treating GBM. FUS has been demonstrated to enhance anti-tumor immunity by the recruitment and activation of immune effectors, and to reduce tumor burden in a mouse GBM model.

Travis Tierney, MD, PhD | Imperial College London

Image-guided high-energy focused ultrasound is a method for introducing non-ionizing energy deep into the brain without a craniotomy and may be especially useful in a number of pediatric conditions where alternatives to conventional (open, endoscopic or laser) surgery are needed.

Petr Tvrđik, PhD | University of Virginia

The objective of the proposed research is to utilize Focused Ultrasound (FUS) to target and treat cerebral cavernous malformations (CCM) in a mouse model of the disease.

Hong-Jian Wei, PhD | Columbia University

With the advancement of ultrasound technology and the feasibility of clinical applicability, there is an emerging need for research to advance the field. Our study provides preclinical rationales for testing the combination of FUS-mediated BBB opening with etoposide in GBM patients.

Kuo Chen Wei, MD | Chang Gung Memorial Hospital

Neuronavigation-guided focused ultrasound can effectively enhance the delivery of chemotherapeutic agents and improve tumor control.

Psychiatric Disorders

Bianca Dang | University of California, Los Angeles

tFUS is a new and non-invasive neuromodulation technique that can selectively target deeper regions of the brain, extending the bounds of current non-invasive neuromodulation treatment techniques. We show this via selectively increasing AG perfusion via tFUS targeting.

Benjamin Davidson, MD | Sunnybrook Research Institute

MRgFUS capsulotomy is an extremely promising treatment option for severe psychiatric illness. Despite being minimally invasive, it can effectively interrupt aberrant limbic circuitry, resulting in widespread metabolic normalization throughout the brain.

Stephen Lee, MS, MPhil | Columbia University

Treatments of neuropathic pain are still limited in scope and efficiency. Moreover, pain has several complex pathways as it travels from the periphery to the brain. We show that FUS can subdue pain at the PNS level, paving the way for more targeted and noninvasive therapies.

Jeong-Ho Seok, MD, PhD | Gangnam Severance Hospital, Yonsei University College of Medicine

Low intensity transcranial focused ultrasound stimulation of the left dorsolateral prefrontal cortex may be a safe and effective treatment option for patients with major depressive disorder.

Norman M. Spivak | University of California, Los Angeles

Transcranial focused ultrasound to the right amygdala has the potential to be a disruptive new modality for the treatment of anxiety disorders. Data is presented regarding the ability of tFUS to change negative reactivity and cognitive reappraisal capabilities.

Neurodegenerative Disorders

Jin Woo Chang | Yonsei University College of Medicine

Additional studies examining the combination of BBB opening with other therapeutic agents, such as antibodies or stem cells, to enhance the beneficial effects of BBB opening for AD patients will be necessary.

Juergen Goetz, PhD | The University of Queensland

Therapeutic ultrasound applied with microbubbles is a treatment modality to improve cognition in brain diseases, with amyloid-beta being an easier therapeutic target than tau. Therapeutic ultrasound is also a modality to improve cognition in physiological ageing.

Maria Eleni Karakatsani | Columbia University

Bilateral sonication significantly ameliorates Alzheimer's pathology and improves the spatial memory of transgenic animals with complex AD phenotype.

Vibhor Krishna, MBBS, SM | OSU Wexner Medical Center

Reversible and focal BBB opening with FUS was safe and feasible in Alzheimer's Disease patients.

Taylor Kuhn | University of California, Los Angeles

tFUS can selectively increase regional blood flow, modulate functional connectivity, and possibly affect associated cognitive performance in the targeted subcortical brain region.

Gerhard Leinenga | The University of Queensland

Focused ultrasound can be used to deliver aducanumab to the brain which improves memory function and lowers plaque burden in a mouse model of Alzheimer's Disease.

Ying Meng, MD | Sunnybrook Research Institute

Blood-brain barrier opening of multiple distributed brain regions with transcranial MR-guided focused ultrasound can be precisely achieved and reasonably tolerated in a single sitting for patients with Alzheimer's disease without any serious adverse events.

Nick Todd | Brigham and Women's Hospital

FUS-BBB opening can safely deliver AAV vectors into the brain of a Huntington's disease mouse model, with the promise of delivering a gene therapy micro-RNA targeted to lowering the expression of the neurotoxic mutant huntingtin protein that is the root cause of this disease.

Kristiana Xhima | Sunnybrook Research Institute

MRlgFUS-induced BBB opening is a promising approach for noninvasive drug delivery to the basal forebrain. MRlgFUS-mediated delivery of TrkA-specific ligands represents a novel therapy that can restore cholinergic neurotransmission and cognition in a preclinical model of AD.

Blood-Brain Barrier Opening and Drug Delivery

Avinoam Bar-Zion | California Institute of Technology

Air-filled proteins allow genetically engineered tumor-homing bacteria and mammalian cells to be remotely detonated with ultrasound. Gas vesicle cavitation enables triggered payload release and propulsion and produces controlled damage to surrounding cells and tissue.

Chenchen Bing | University of Calgary

The feasibility of blood-nerve barrier (BNB) disruption has been demonstrated using focused ultrasound and microbubbles in a rodent model. A higher dosage of microbubble might be required compared to the brain to achieve BNB disruption.

Juan Castillo, PhD | University Hospital of Cologne

HIFU-Hyperthermia using TSLs is a suitable method for local drug release of doxorubicin & cisplatin in large animals. This method is suitable to treat tumors such as sarcomas located in non-moving regions and is a promising step towards clinical translation.

Jin Woo Chang | Yonsei University College of Medicine

Additional studies examining the combination of BBBD with other therapeutic agents, such as antibodies or stem cells, to enhance the beneficial effects of BBBD for AD patients will be necessary.

Bingbing Cheng, PhD | University of Calgary

It is feasible to perform non-invasive targeted brain mild hyperthermia in small animal models with MR-guided focused ultrasound. The introduction of microbubbles can reduce the ultrasound power required for hyperthermia and potentially improve the safety.

Christian Coviello, PhD | OxSonics Therapeutics

Penetration of drugs into and throughout solid tumors is recognized as a major limitation to their effectiveness. SonoTran is a drug agnostic solution requiring no reformulation. This work validates the preclinical safety and performance of the system leading to clinical trial.

Daniel Dahis, MSc | Technion Institute of Technology

Copper Oxide nanoparticle (NP) accumulation in the brain following FUS-mediated BBB disruption induced an increase in contrast to noise ratio of the targeted tissue on MRI. This effect can be leveraged for the development of CuO NP-based theranostic agents for tumor imaging and treatment.

Zachary Englander | Columbia University

Focused ultrasound mediated blood-brain barrier opening is safe and feasible following radiotherapy in a murine diffuse intrinsic pontine glioma model.

Michael Gray, PhD | University of Oxford

The TarDox study confirmed the safety and feasibility of USgFUS-mediated mild hyperthermia for drug release within oncologically relevant volumes. This approach may be applied to a range of thermally-activated chemotherapeutics and tumour indications, including pancreatic cancer.

Robin Ji, MS | Columbia University

The results presented in this study suggest a relationship between cavitation signals and the immune response to FUS-induced BBB opening, which ultimately may be used to modulate the immune response for more effective therapies.

Noé Jiménez, PhD | Universitat Politècnica de València

We demonstrate that contactless particle trapping can be performed through the skull bones using acoustic holograms. The benefit is twofold: holograms allow the generation of the vortex trap using low-cost system; and the skull aberrations can be compensated.

Sergio Jimenez Gambin | Universitat Politècnica de València

We demonstrate how a single-element transducer with a 3D-printed holographic lens allows (1) simultaneous production of bilateral BBB opening in anesthetized mice in vivo, and (2) compensation of the aberrations due to both the skull and the water cone.

Maria Eleni Karakatsani | Columbia University

Bilateral sonication significantly ameliorates Alzheimer's pathology and improves the spatial memory of transgenic animals with complex AD phenotype.

Maria Eleni Karakatsani | Columbia University

Diffusion tensor imaging may be used in the clinic for detecting BBB opening following FUS treatment and/or to evaluate BBB integrity in brain-related pathologies.

Chulyong Kim | Georgia Institute of Technology

Ultrasonic thermal stress promotes acute changes in the transvascular transport dynamics in brain tumors and promotes the delivery of chemotherapy encapsulated in heat sensitive nanoparticles.

Alina Kline-Schoder | Columbia University

In this study, infiltration of macrophages was detected 24 hours after BBB opening.

Uday Kumar | Stanford University

Ultrasound in the presence of microbubbles can trigger non-destructive widening of intercellular spaces between blood vessel epithelial cells and increase the penetration of microRNAs loaded nanoparticles for improved therapeutic outcome.

Asis Lopez, PhD | U.S. Food and Drug Administration

The outcomes of these in vivo experiments are expected to assist in predicting the rupture probability for HIFU + Microbubble procedures.

Vibhor Krishna, MBBS, SM | OSU Wexner Medical Center

Reversible and focal BBB opening with FUS was safe and feasible in Alzheimer's Disease patients.

Benoit Larrat, PhD | Commissariat à l'Energie Atomique et aux Energies Alternatives

In a rat syngenic brain tumor model, FUS induced BBB opening significantly enhances delivery and efficacy of a cocktail composed of anti-PD1 antibody together with drugs limiting pro-tumoral inflammation.

Benoit Larrat, PhD | Commissariat à l'Energie Atomique et aux Energies Alternatives

FUS and MB significantly increase the delivery of cetuximab across the BBB. PET is a powerful method to assess the pharmacokinetics of the passage of mAb through the BBB. 89Zr-DFO-CTX was synthesized and used to quantify the enhancement of brain exposure to CTX.

Gerhard Leinenga | The University of Queensland

We show unique microglia responses to opening of the blood brain barrier by focused ultrasound in plaque-bearing mouse model of Alzheimer's Disease.

Tamotsu MARUYAMA | Teikyo University

We developed lipid microbubbles (LMBs) that are more stable in blood flow by using DSPG. The optimal DSPG content was about 60% in the lipid shell of LMBs. LMBs with DSPG could be applicable for development of an effective ultrasound diagnostic and therapeutic system.

Ying Meng, MD | Sunnybrook Research Institute

Blood-brain barrier opening of multiple distributed brain regions with transcranial MR-guided focused ultrasound can be precisely achieved and reasonably tolerated in a single sitting for patients with Alzheimer's disease without any serious adverse events.

Kaylee Meyers | Michigan Technological University

To accelerate repair in tendon tissue, our group has developed an injectable adhesive hydrogel containing fibrin x-particles with the capacity for thermal and mechanical controlled release of nitric oxide, an antimicrobial signaling molecule that influences ECM turnover, via FUS.

Sophie Morse | Imperial College London

By emitting ultrasound in a rapid short-pulse (RaSP) sequence we can open the blood-brain barrier in a safer way with less microglial activation and a reduced amount of blood-borne substances entering the brain.

Daiki Omata | Teikyo University

The effect of lipid-based microbubbles (LBs) containing various gases on ultrasound (US) triggered drug delivery to the brain was examined. The treatment of LBs containing perfluoropropane or perfluorobutane with US showed efficient drug delivery to the brain.

Kota Ono | Tokyo University of Pharmacy and Life sciences

By loading miRNA on nanobubbles coated with cationic polysaccharides, efficient miRNA delivery after systemic injection is possible using ultrasound.

Mehmet Ozdas, PhD | ETH Zurich

FUS and microbubbles induced BBB opening causes micro-seizure like activity in the brain and induces inhibition of evoked local field potentials.

Frederic Padilla | Focused Ultrasound Foundation

Ultrasound molecular imaging (USMI) can be used to plan ultrasound-triggered drug delivery and to monitor treatment at the anatomical, functional and molecular levels. USMI-guided cavitation ultrasound can potentiate liposomal doxorubicin.

So Hee Park, PhD | Yonsei University College of Medicine

The survival rate up to 1 year was 100% in six patients who underwent BBBD for GBM. The median PFS in patients with recurrence was 13.5 months. None of the patients had immediate or delayed BBBD-related complications.

Antonios Pouliopoulos, PhD | Columbia University

Neuronavigation-guided FUS allows bedside brain treatments without the need of on-line MRI guidance and with minimal focal distortions or skull heating. Additionally, clinically-relevant FUS-mediated BBB opening may lead to a reversible immune response and cognitive improvement.

Richard Price, PhD | University of Virginia

We unveil a critical role for adaptive immunity in the efficacy of the combination of FUS and GEM against breast cancer. These findings generate support for translating the FUS + GEM combination to clinical trials for women with metastatic breast cancer.

Richard Price, PhD | University of Virginia

The underlying transcriptomic response to FUS-mediated blood-brain barrier disruption may be strongly influenced by the choice of anesthetic. Such responses may synergize and/or conflict with responses generated by the therapeutic approach itself.

Richard Price, PhD | University of Virginia

We develop and report a computational fluid dynamic model of the BBB capable of mimicking the influence of FUS-mediated BBB and antibody delivery by altering the intrinsic permeability of the endothelial lipid bilayer.

Richard Price, PhD | University of Virginia

Cells of the NVU (neurons, astrocytes, microglia, endothelial cells, pericytes, and oligodendrocytes) are differentially transfected and transcriptomically impacted by low vs high PNP in the context of FUS mediated BBB disruption.

Richard Price, PhD | University of Virginia

We demonstrate the capacity of FUS to enhance delivery of exogenous mitochondria into infarcted brain tissue following ischemic stroke.

Richard Price, PhD | University of Virginia

We develop a Boolean logic-based model for brain endothelial cell signaling which we use to predict how transcriptomic changes, resulting from FUS treatment of the brain, could impact BBB integrity.

Maryam Siddiqui | University of Calgary

Using MRI guided focused ultrasound, non-invasive and precise induction of localized hyperthermia in small animals can be achieved. Coupling this with encapsulated-drug in thermosensitive liposomes can potentially improve targeted drug-delivery in tumor of small rodent models.

Juliette Strubel | Focused Ultrasound Foundation

We provide an overview of the various classes and sizes of therapeutics that have successfully crossed the BBB with ultrasound and summarize these findings in a comprehensive illustration and video.

Ivan M. Suarez Castellanos, PhD | INSERM

Focused Ultrasound (FUS) is capable of modulating the inherent electrical activity and properties of individual neurons while also triggering new activity in the form of perturbations to the cell membrane potential. The stimulated activity can be either immediate or delayed.

Yuno Suzuki | Teikyo University

We developed an anticancer drug delivery system with doxorubicin encapsulated liposomes-loaded microbubbles and ultrasound. In this combination, the doxorubicin was effectively delivered to pancreatic cancer cells and cell growth suppression was observed.

Jerzy Szablowski, PhD | Rice University

We developed a new viral vector that improves the efficiency and tissue-specificity of gene delivery to the brain when used in conjunction with FUS-BBBO. We engineered this new vector, which we called AAV.FUS, using high-throughput capsid mutation and in vivo screening methods.

Nick Todd | Brigham and Women's Hospital

FUS-BBB opening can safely deliver AAV vectors into the brain of a Huntington's disease mouse model, with the promise of delivering a gene therapy micro-RNA targeted to lowering the expression of the neurotoxic mutant huntingtin protein that is the root cause of this disease.

Chih-Hung Tsai, PhD | NaviFUS Co. Ltd.

We developed a real-time acoustic emission feedback control algorithm that can be implemented on NaviFUS system to monitor and control the procedure in real-time.

Hong-Jian Wei, PhD | Columbia University

With the advancement of ultrasound technology and the feasibility of clinical applicability, there is an emerging need for research to advance the field. Our study provides preclinical rationales for testing the combination of FUS-mediated BBB opening with etoposide in GBM patients.

Kuo Chen Wei, MD | Chang Gung Memorial Hospital

Neuronavigation-guided focused ultrasound can effectively enhance the delivery of chemotherapeutic agents and improve tumor control.

Beat Werner, MSc. | University Children's Hospital Zurich

Dedicated FUS system carrying a central ultrasound imaging probe, and a suitably positioned, acoustically transparent cranial substitute serving as an acoustic keyhole, might enable ultrasound-guided, frameless interventions for opening the BBB in deeplying brain tumors.

Claire Wunker, MD | Luenfeld-Tanenbaum Research Institute

Rhabdomyosarcoma requires new treatments to improve survival and decrease long term side effects. TLD with MRgHIFU is a promising treatment combination. We found higher doxorubicin levels in the tumor after 20 minutes of heating compared to controls in a murine RMS model.

Dezhuang Ye, PhD Candidate | Washington University in Saint Louis

This study found FUS + intranasal drug delivery efficiency depends on several key experimental parameters, including the time delay between intranasal administration & FUS sonication, the FUS pressure, and the waiting time to sacrifice the mouse post-FUS.

Yuana Yuana, PhD | Technical University of Eindhoven

US microbubbles triggered the release of extracellular vesicles (EV) containing CTG or BSA FITC in the cell supernatant after treatment, and the amount of EV released correlated with increases in acoustic pressure. These EVs were taken up within 4h after co-culturing with tumor cells.

Neuromodulation

William Apoutou N'Djin | INSERM

FUS exposures can trigger Ca²⁺ fluxes whose spatial-temporal dynamics can be studied at the cell scale in in-vitro human neural networks, using a mixed FUS / Fluorescence microscopy research platform.

David Attali, MD, PhD Student | Physics for Medicine Paris, INSERM, ESPCI Paris, CNRS, PSL Research University Université de Paris, GHU Paris

Using Transcranial Ultrasound Stimulation directed toward oculomotor regions, we provide evidence for sustained, reversible, and specific modulation of oculomotor behavior in non-human primates and quantify the return to baseline (20 min).

Bashar Badran, PhD | Medical University of South Carolina

Transcranial focused ultrasound (tFUS) is a promising, noninvasive, and focal method of stimulating deep in the brain. tFUS to stimulate the anterior thalamus produced antinociceptive effects on heat pain threshold. Further tFUS investigation is warranted.

Xinghao Cheng | University of Oxford

We use ultrasound simulations to demonstrate targeting of the hippocampus for transcranial ultrasound stimulation (TUS) using a single element transducer with a lens. The simulations employ geometries from subject-specific MRIs and at 500 kHz the focal volume is $< 30 \text{ mm}^3$.

John Cressman, PhD | George Mason University

We computationally model the effects of the acoustic radiation force on neuronal tissue. The model is able to reproduce experimental results and provide a detailed explanation of the mechanisms of action.

Bianca Dang | University of California, Los Angeles

tFUS is a new and noninvasive neuromodulation technique that can selectively target deeper regions of the brain, extending the bounds of current techniques. We show this via selectively increasing AG perfusion via tFUS targeting.

Jake Hesselink, Bsc | University of Calgary

The delivery of FUS for non-invasive neuromodulation produces measurable vibrations at the skull, likely linked to the pulse repetition frequency (PRF) of the signal. Further study should attempt to avoid the auditory artifact by adjusting PRF, and investigate the mechanism underlying motor responses to FUS.

Xuandi Hou | The Hong Kong Polytechnic University

We developed an ultrasonic mechanogenetic tool to manipulate neuronal activity and signaling with excellent precision by introducing nano-materials.

Hyun-Chul Kim | Brigham and Women's Hospital

Pulsed low-intensity transcranial FUS can safely & temporarily modulate regional-specific brain functions in awake sheep.

Vibhor Krishna, MBBS, SM | OSU Wexner Medical Center

Thermal neuromodulation was observed in a minority of subthreshold sonications. Higher temperatures and bigger spot sizes were associated with thermal neuromodulation.

Taylor Kuhn | University of California, Los Angeles

tFUS can selectively increase regional blood flow, modulate functional connectivity, and possibly affect associated cognitive performance in the targeted subcortical brain region.

Stephen Lee, M.S., M.Phil. | Colombia University

Treatments of neuropathic pain are still limited in scope and efficiency. Moreover, pain has several complex pathways as it travels from the periphery to the brain. We show that FUS can subdue pain at the PNS level, paving the way for more targeted and noninvasive therapies.

Pierre Mourad, PhD | University of Washington

Ultrasound capable of activating central neurons can also activate oligodendrocytes and microglia to therapeutic effect in mouse models of multiple sclerosis and of Alzheimer's Disease, respectively.

Pavel Novak, PhD | Storz Medical AG

Shockwaves are a special, unique form of ultrasound with high pressure amplitudes and very short durations. They have been used in medicine since 1980 for stone disintegration and soft tissue stimulation and regeneration.

Jeong-Ho Seok, MD, PhD | Gangnam Severance Hospital, Yonsei University College of Medicine

Low intensity transcranial focused ultrasound stimulation of the left dorsolateral prefrontal cortex may be a safe and effective treatment option for patients with major depressive disorder.

Lin Song, PhD | The Hong Kong Polytechnic University

We use ultrasound simulations to demonstrate targeting of the hippocampus for transcranial ultrasound stimulation (TUS) using a single element transducer with a lens. The simulations employ geometries from subject-specific MRIs and at 500 kHz the focal volume is $< 30 \text{ mm}^3$.

Ivan M. Suarez Castellanos, PhD | French National Institute of Health and Medical Research

Focused Ultrasound (FUS) is capable of modulating the inherent electrical activity and properties of individual neurons while also triggering new activity in the form of perturbations to the cell membrane potential. The stimulated activity can be either immediate or delayed.

Lennart Verhagen | Radboud University

Long-lasting non-invasive modulation of neural activity and behaviour is now possible in primates using low-intensity focused ultrasound. This opens up exciting new possibilities for the development of novel targeted treatment options in human neurology and psychiatry.

Yaoheng Yang | Washington University in St. Louis

This work establishes that TRPV1-based sonogenetics enables noninvasive, cell-type specific, precisely controlled modulation of mammalian neuronal activity in vivo.

Hsiang-Yu Yu, MD | Taipei Veterans General Hospital

Low intensity focused ultrasound targeting epileptogenic zones for neuromodulation with simultaneous intracranial EEG recording was done in four cases. EEG showed band power changes during and after treatment. No unanticipated side effects or lesioning effects on MRI were reported.

Jiejun Zhu | The Hong Kong Polytechnic University

Ultrasound neuron modulation is mediated by piezo1 in vitro. This result also suggests a possible mechanism for in vivo modulation. By controlling the expression of piezo1 we may able to target specific neuronal pathways or nuclei for study in both basic and clinical neurosciences.

Epilepsy

Vibhor Krishna, MBBS, SM | OSU Wexner Medical Center

Unilateral anterior thalamic nucleus ablation using focused ultrasound is feasible for patients with intractable partial-onset epilepsy. Detailed neuro-psychological assessment is important to detect changes in memory and mood.

Hsiang-Yu Yu | Taipei Veterans General Hospital

Low intensity focused ultrasound targeting epileptogenic zones for neuromodulation with simultaneous intracranial EEG recording was done in four cases. EEG showed band power changes during and after treatment. No unanticipated side effects or lesioning effects on MRI were reported.

Movement Disorders

Abdul-Kareem Ahmed, MD | University of Maryland School of Medicine

Unilateral MR-guided focused ultrasound thalamotomy has lower treatment requirements than unilateral pallidotomy. This reflects the treatment envelope of current systems. These findings can inform patient selection and treatment planning for new, peripheral cerebral targets.

Steven P. Allen | University of Virginia

Experiments in a preclinical model demonstrate that MRI diffusion weighted imaging can detect thermal ablation in the thalamus within minutes after treatment.

Ayesha Jameel, DPMSA, BSc, MBBS, FRCR | Imperial College

In this pilot study, bilateral MRgFUS treatment for refractory essential tremor has proven to be safe and effective with no persistent adverse effects at 12 months. Further studies are needed with detailed analysis on the effect of bilateral MRgFUS treatments on speech.

Ayesha Jameel, DPMSA, BSc, MBBS, FRCR | Imperial College

Targeting VIM and ZI in the same procedure provides both contralateral and ipsilateral effects. VIM plus ZI provides additional tremor suppression compared to VIM alone. Spot elongation should be considered when targeting deeper tissues.

Vibhor Krishna, MBBS, SM | OSU Wexner Medical Center

The lesion mapping technique proved useful in localizing tremor network. Functional connectivity in the tremor network was significantly higher in essential tremor patients. Therapeutic FUS ablation restored functional connectivity in the tremor network.

Raul Martinez Fernandez, MD, PhD | CINAC, Hospital Universitario HM Puerta del Sur, Móstoles, Universidad CEU-San Pablo, Madrid, Spain

Staged focused ultrasound bilateral thalamotomy might be safe and effective for the treatment of essential tremor.

Catherine Swytink-Binnema, MSc | University of Calgary

Although the thalamic Vim nucleus is involved in proprioception, proprioceptive changes following MRgFUS Vim thalamotomy have never been quantified. Using the Kinarm exoskeleton robot, we show that proprioception does not significantly change following Vim thalamotomy.

Cancer Immunotherapy

Mohamad Abedi | California Institute of Technology

We engineered gene circuits providing transient & sustained activation of gene expression in T-cells in response to brief thermal stimuli, demonstrating using these circuits to control the secretion of a therapeutic gene, expression of a CAR, & killing tumor cells.

Harshini Ashar | Oklahoma State University

FUS can be used for non-invasive treatment of spontaneously occurring canine cancers. FUS ablation of solid tumors can also enhance the local and systemic populations of anti-tumoral macrophages and activated T-cells to improve immunity against cancer.

Parwathy Chandra, PhD | National Institute of Health

This study demonstrates the immunomodulatory potential of non-ablative pulsed focused ultrasound in altering an antiinflammatory, tumor microenvironment towards a pro-inflammatory, anti-tumor landscape by engaging both innate and adaptive arms of immunity.

Clifford Cho, MD | University of Michigan Medical School

Non-thermal focused ultrasound ablation induces a stronger systemic immunostimulatory response than thermal focused ultrasound ablation.

Gadi Cohen | National Institute of Health

Temporal alterations of non-ablative pulsed focused ultrasound exposure display a pro-inflammatory proteomic profile within the tumor microenvironment, thus underscoring the potential use of pFUS as neoadjuvant treatment approaches in cancer immunotherapy.

Lynn Dengel, MD, MSc | University of Virginia

The presented trial of FUS ablation of metastatic solid tumors with/without systemic therapy has obtained FDA approval. 2/32 participants have enrolled and received FUS without immediate complications. Data analysis will evaluate changes in the tumor microenvironment.

Patrick Dillon, MD | University of Virginia

FUS combined with checkpoint inhibitor therapy appears to be safe in metastatic breast cancer. Immunologic outcomes suggest that a degree of local and systemic modulation occurs. The impact on long-term outcomes is unknown.

Avinash Eranki, PhD | Indian Institute of Technology, Hyderabad

Boiling histotripsy (BH) mechanically fractionates neuroblastoma tumors, resulting in a significant intratumoral infiltration of immune cells compared to untreated neuroblastoma tumors.

Avinash Eranki, PhD | Indian Institute of Technology, Hyderabad

Mechanical fractionation using boiling histotripsy induces systemic immune sensitization in an established and refractory murine neuroblastoma model, opening a window for effective immunotherapy that promises a novel yet efficacious immuno-adjuvant modality to overcome therapeutic resistance.

David Goertz, PhD | Department of Medical Biophysics, University of Toronto

In this work, we demonstrated that ultrasound stimulated microbubbles can profoundly enhance the clinical drug combination of anti-PD-L1 + paclitaxel in the treatment of murine triple negative breast cancer.

Robin Ji, MS | Columbia University

The results presented in this study suggest a relationship between cavitation signals and the immune response to FUS-induced BBB opening, which ultimately may be used to modulate the immune response for more effective therapies.

Alina Kline-Schoder | Columbia University

In this study, infiltration of macrophages was detected 24 hours after BBB opening.

Benoit Larrat, PhD | Commissariat à l'Energie Atomique et aux Energies Alternatives

In a rat syngenic brain tumor model, FUS induced BBB opening significantly enhances delivery and efficacy of a cocktail composed of anti-PD1 antibody together with drugs limiting pro-tumoral inflammation.

Benoit Larrat, PhD | Commissariat à l'Energie Atomique et aux Energies Alternatives

FUS and MB significantly increase the delivery of cetuximab across the BBB. PET is a powerful method to assess the pharmacokinetics of the passage of mAb through the BBB. 89Zr-DFO-CTX was synthesized and used to quantify the enhancement of brain exposure to CTX.

Anirudh Natarajan | University of California, Berkeley

Automated post-processing of imaging data will rapidly speed up and simplify analysis allowing researchers to focus on optimizing their experimental preparations. Creating an analysis pipeline in Python will also capitalize on the most current image analysis algorithms.

Antonios Pouliopoulos, PhD | Columbia University

Neuronavigation-guided FUS allows bedside brain treatments without the need of on-line MRI guidance and with minimal focal distortions or skull heating. Additionally, clinically-relevant FUS-mediated BBB opening may lead to a reversible immune response and cognitive improvement.

Richard Price, PhD | University of Virginia

We develop and report a computational fluid dynamic model of the BBB capable of mimicking the influence of FUS-mediated BBB opening and antibody delivery by altering the intrinsic permeability of the endothelial lipid bilayer.

Richard Price, PhD | University of Virginia

Through computational simulation of the glymphatic system, we demonstrate that augmentation of perivascular spaces during FUS-induced blood-brain barrier opening is predicted to increase solute clearance.

Richard Price, PhD | University of Virginia

Opening the blood-tumor barrier in intracranial melanoma with focused ultrasound (i) elicits transcripts associated with inflammation, (ii) increases antigen within the tumor, and (iii) contributes to dendritic cell maturation. Nonetheless, the response is mild and transient.

Richard Price, PhD | University of Virginia

Through computational simulation of the glymphatic system, we demonstrate that augmentation of perivascular spaces during FUS-induced blood-brain barrier opening is predicted to increase solute clearance.

Ashish Ranjan, B.V.Sc, PhD | Oklahoma State University

Encapsulation of doxorubicin in thermally sensitive liposomes, and its combination with local focused ultrasound heating of solid tumors, can improve local and systemic chemo-immunotherapy of colon cancer.

Sri Nandhini Sethuraman, PhD | Oklahoma State University

Local focused ultrasound heating along with intratumoral anti-CD-40 agonist antibody therapy improves T cell recruitment, preserves T cell function, and suppresses the treated and untreated murine melanoma tumor growth rate.

Sri Nandhini Sethuraman, BVSc, AH, MVSc | Oklahoma State University

Combination of boiling histotripsy (BH) and anti-CD40 agonistic antibody transforms the immunologically cold murine melanoma into an activated one, resulting in an improved sensitization to immune checkpoint inhibitors and antitumor effects.

Tao Sun, PhD | Brigham and Women's Hospital, Harvard Medical School

Our results provide preclinical proof-of-principle for pairing FUS with PD-1 blockade therapy in treating GBM. FUS has been demonstrated to enhance anti-tumor immunity by the recruitment and activation of immune effectors, and to reduce tumor burden in a mouse GBM model.

Ryo Suzuki | Faculty of Pharma-Science, Teikyo University

We induced an effective antitumor immune response by combining sonotherapy and dendritic cell (DC)-based immunotherapy. Sonotherapy induced immunomodulation in tumor tissue and enhanced the effect of DC-based immunotherapy.

Prostate

Sandeep Arora, MBBS | Vanderbilt University Medical Center

Two-year follow-up of MRI-guided transurethral ultrasound ablation (TULSA) in men with localized prostate cancer demonstrates effective disease control with low toxicity and stable quality of life.

Nikolas Evripidou | Cyprus University of Technology

MRI guided positioning device using focused ultrasound for treatment of prostate cancer is described.

Yoni Hertzberg, PhD | NINA Medical

A new method of real-time US imaging of a HIFU field is evolving. The method can be used safely during USgHIFU procedures to provide a live image of the treatment beam to the practitioner as well as focal point tracking and improvement in treatment efficacy and safety.

Robert Lemme | A.T. Still University, Kirksville College of Osteopathic Medicine

HIFU is a safe and effective treatment option for prostate cancer that can be applied in the community setting with excellent potency and continence preservation along with good short-term disease control.

Frederic Padilla | Focused Ultrasound Foundation

Ultrasound molecular imaging (USMI) can be used to plan ultrasound-triggered drug delivery and to monitor treatment at the anatomical, functional and molecular levels. USMI-guided cavitation ultrasound can potentiate liposomal doxorubicin.

Thomas Payen, PhD | INSERM

Higher performance in lesion monitoring is needed for widespread use of focal HIFU treatments in prostate cancer. Passive elastography can be modified to provide stiffness maps using slow-rate B-mode images acquired on a conventional clinical ultrasound systems which can be used to guide treatment.

Deepika Reddy | Imperial Prostate

In select patients with non-metastatic prostate cancer, focal therapy achieves similar medium-term oncological outcomes to radical prostatectomy.

Deepika Reddy | Imperial Prostate

Focal ablative salvage therapy produces good medium term cancer control, with minimal severe complications, in patients with radio-recurrent localised prostate cancer.

George Schade, MD | University of Washington, Department of Urology

Transrectal boiling histotripsy (BH) of the prostate is feasible with a pre-clinical device. Both canine and human tissue are susceptible to BH, though human tissue may be more resistant. Future studies will examine treatment optimization and resistance mechanisms.

Sunao Shoji, MD, PhD, MBA | Tokai University School of Medicine

Accurate focal therapy was performed with HIFU based on the locations of mpMRI-visible csPCa. Follow-up biopsy was avoided in the patients who had PI-RADS category <3 and PSAD <0.068 ng/mL after the treatment. Post-procedural ED and ejaculation were 86% and 70%.

Breast Tumors

Sandeep Arora, MBBS | National Institute of Health

This study demonstrates the immunomodulatory potential of non-ablative pulsed focused ultrasound in altering an antiinflammatory, tumor microenvironment towards a pro-inflammatory, anti-tumor landscape by engaging both innate and adaptive arms of immunity.

Gadi Cohen | National Institute of Health

Temporal alterations of non-ablative pulsed focused ultrasound exposure display a pro-inflammatory proteomic profile within the tumor microenvironment, thus underscoring the potential use of pFUS as neoadjuvant treatment approaches in cancer immunotherapy.

Patrick Dillon, MD | University of Virginia

FUS combined with checkpoint inhibitor therapy appears to be safe in metastatic breast cancer. Immunologic outcomes suggest that a degree of local and systemic modulation occurs. The impact on long-term outcomes is unknown.

David Goertz, PhD | Department of Medical Biophysics, University of Toronto

In this work, we demonstrated that ultrasound stimulated microbubbles can profoundly enhance the clinical drug combination of anti-PD-L1 + paclitaxel in the treatment of murine triple negative breast cancer.

Kenneth Hoyt | University of Texas at Dallas

Multifocused ultrasound therapy spatially enhances microvascular permeabilization and represents a promising approach for improved drug delivery and accumulation in the cancerous mass.

Xiaoyue Li, MS | Columbia University

We show that Harmonic Motion Imaging (HMI) can be used to monitor Focused Ultrasound Surgery (FUS) ablation in mammary breast tumors in mice using simultaneous 2D imaging for the first time.

Ying Meng, MD | Sunnybrook Research Institute

In this study, we will investigate the safety and feasibility of MRgFUS induced BBB opening for trastuzumab delivery for intracranial metastatic lesions in Her2-positive breast cancer patients.

Richard Price, PhD | University of Virginia

We unveil a critical role for adaptive immunity in the efficacy of the combination of FUS and GEM against breast cancer. These findings generate support for translating the FUS + GEM combination to clinical trials for women with metastatic breast cancer.

Liver, Pancreas, Kidney, Colorectal, Head & Neck Tumors

Irving C. Allen | Virginia Maryland College of Veterinary Medicine

These data support the feasibility of using the immunocompromised pig model for the design and evaluation of clinically relevant, novel medical devices to treat pancreatic cancer and beyond.

Alissa Hendricks | Virginia Polytechnic Institute and State University

The current work shows specific DAMPs and immune cell populations responding to histotripsy ablation of pancreatic cancer in vitro and in vivo, showing similar or improved effects when compared to established ablation modalities.

Jordan Joiner | The University of North Carolina at Chapel Hill

Low-intensity focused ultrasound and microbubbles can transiently increase immune cell infiltration in murine pancreatic tumors and draining lymph nodes. In future studies, this treatment will be combined with immunotherapy.

Vera Khokhlova | University of Washington

Mechanical ablation of tissue volumes with real-time ultrasound control of the degree of tissue liquefaction is feasible using boiling histotripsy (BH) technology combined with electronic focus steering and Doppler-type imaging.

Tatiana Khokhlova | University of Washington

Inertial cavitation produced by pulsed high intensity focused ultrasound in pancreas tumors may be a promising therapy that would not only enhance chemotherapeutic drug concentration in the tumor but also reduce the tumor chemoresistance and immunosuppressive microenvironment.

Kisoo Kim, PhD | University of California, San Francisco

Motion-robust, multi-slice, real-time MR thermometry was developed to monitor ultrasound thermal therapy in abdominal organs. This all-in-one MR thermometry is available for accurate and stable temperature measurements in abdominal organs.

Uday Kumar | Sanford University

Ultrasound in the presence of microbubbles can trigger non-destructive widening of intercellular spaces between blood vessel epithelial cells and increase the penetration of microRNAs loaded nanoparticles for improved therapeutic outcome.

David Melodelima, PhD | LabTAU

We demonstrated in 35 patients that the use of an ultrasound-guided intra-operative toroidal HIFU transducer was feasible, safe and effective in ablating liver metastases with safety margins. The sonication time was 6 minutes.

David Melodelima, PhD | LabTAU

An intraoperative HIFU treatment at the pancreas-mesenteric artery interface was shown to be safe and feasible without vascular thrombosis using a toroidal HIFU transducer under Doppler guidance.

Petros Mouratidis, PhD | The Institute of Cancer Research London

Heating can be combined with therapies targeted against the heat shock response to provide a synergistic cytotoxic effect against various cancer cell types. The mutational status of client proteins may predict which cell types respond to these treatments.

Petros Mouratidis, PhD | The Institute of Cancer Research London

pHIFU treatments using "low" rarefactional pressures combined with microbubbles can induce acoustic cavitation in pancreatic tumors and decrease tumor growth. It is under investigation whether these treatments could also mount an effective anti-cancer immune response.

Kaitlyn Perry, BSc | Sunnybrook Health Sciences Center, University of Toronto

We have created a workflow and software solution that can be applied to diagnostic MRIs prior to having patients on the MR-HIFU tabletop, reducing treatment time and cost. Virtual MR-HIFU planning is feasible and can be used in future studies of primary rectal and other tumors.

Samuel Pichardo | University of Calgary

Hyperthermia treatment of locoregional head and neck tumors with MRlgFUS and radiation therapy is feasible and safe with adequate patient selection and intra-operative communication with the patient and the team.

Shashank Sirsi, PhD | The University of Texas at Dallas

Focused ultrasound therapy with microbubble contrast agents significantly improves liposomal doxorubicin uptake in neuroblastoma. Tumor perfusion can help predict when they are most amenable to drug uptake and help monitor therapy.

Shashank Sirsi, PhD | The University of Texas at Dallas

Nanoparticle drug delivery to neuroblastoma with focused ultrasound and microbubbles (sonopermeation) can significantly enhance chemotherapy while minimizing off target effects. 2D and 3D contrast enhanced imaging can help monitor the bioeffects of sonopermeation.

Shashank Sirsi, PhD | The University of Texas at Dallas

HIFU therapy for unresectable pancreatic cancer, when used in combination with chemotherapy, showed significant differences compared with chemotherapy alone, with increased anti-tumor and symptom-relief effects. HIFU therapy has the potential to be a component of new method of combination therapy.

Eleanor Stride | University of Oxford

Sonodynamic therapy offers a new treatment option for recalcitrant tumor for which existing therapeutic options are extremely limited. Its efficacy is significantly enhanced through the use of oxygen microbubbles as a therapeutic adjuvant.

Caitlin Tydings, MD | Children's National Hospital

Boiling histotripsy with immunotherapy has the potential to promote an anti-tumor response. While HIFU thermal ablation did not demonstrate the same findings, further work investigating protumoral factors and other tumor cell lines needs to be performed.

Pete Weber | Virginia Polytechnic Institute and State University Carillion School of Medicine

Histotripsy is capable of successfully ablating both hepatocellular carcinoma tumors and colorectal liver metastases. Higher treatment doses are likely required to achieve complete ablations for intrahepatic cholangiocarcinomas.

Musculoskeletal Disorders

Lauren Arnold | Virginia Polytechnic Institute and State University

Histotripsy is a promising future treatment for primary canine and human osteosarcoma (OS). Feasibility treatments demonstrated successful generation of well-confined histotripsy bubble clouds and cell ablation zones in excised canine OS tissues.

Harshini Ashar | Oklahoma State University

A combination of focused ultrasound heating with antibiotic-laden thermally sensitive liposomes can achieve high microbicide concentrations locally to induce clearance of bone infections, obviating need for long-duration antimicrobial therapies & surgeries.

Joe Baal, MD | UCSF Department of Radiology & Biomedical Imaging

MRgFUS has a favorable safety profile & high efficacy in pain score reduction of symptomatic bone metastases. It may be a viable alternate first option for the palliative treatment of bone metastases in patients with suspected radio-resistant primary cancers.

Juan Castillo, PhD | University Hospital of Cologne

HIFU-Hyperthermia using TSLs is a suitable method for local drug release of doxorubicin and cisplatin in large animals. This method is suitable to treat tumors such as sarcomas located in non-moving regions and is a promising step towards clinical translation.

William Chu Kwan, B.Eng., MD | Hospital for Sick Children

The interaction between MRgFUS boiling histotripsy and ablation can reduce the energy and limit the thermal spread in ablative treatments of ex-vivo tendons, making this method a potential modality to resect tendon contractures in patients with cerebral palsy or stroke.

Alessandro De Maio | Sapienza, Rome University

MRgFUS confirmed significant advancements in pain palliation for bone metastases and, compared to first-line external radiation therapy, provided benefits on: rate, likelihood and degree of improvement, no ionizing radiation-related morbidity & survival.

Aline Desoutter | LabTAU

Radiotherapy decreases bone quality and bone mineral density. A radiation protocol delivering 8.5Gy weekly in five sessions seemed to be valuable for evaluating postextractional bone healing in the rabbit. Low intensity FUS seem to have a positive impact on trabecular number in irradiated bone.

Beatrice Lena | UMC Utrecht

Interleaving fat and water MR thermometry allows temperature monitoring in muscle and fat. This will help create a complete view of the temperature distribution when heating bone lesions and to prevent damage to healthy tissue present in the target area.

Chitra Meduri, MS | Virginia Polytechnic Institute and State University

We designed a custom, image-guided FUS system to identify and characterize FUS regimes capable of producing a range of mechanical, thermal, or combined mechanical-thermal effects in mouse Achilles tendons in vivo, enabling us to study effects of FUS on tendon healing.

Kei Niraswa | Tokyo University of Pharmacy and Life Sciences

We have developed nanobubbles in which ultrasound contrast agent gas is encapsulated in liposomes, and have shown that they can be a useful delivery system in CRISPR-based genome editing for restoring dystrophic skeletal muscle.

Molly Smallcomb, MS | Pennsylvania State University

Highly collagenous tissues, like tendon, have shown resistance to mechanical disruption from focused ultrasound. This study histologically evaluates whether this mechanical disruption is achievable without thermal denaturation in ex vivo rat tendon for therapeutic application.

Norman M. Spivak | University of California, Los Angeles

Sonication of the scapula at 14 W/cm² Ispta does not lead to heating that could potentially be dangerous and cause burns.

Janina Strobel | University of Cologne

Larger multicenter trials with different MR-HIFU systems require standardized treatment protocols to achieve reliable results. To address this issue we developed a reusable bone phantom for comparison of different MR-HIFU treatment protocols.

Caitlin Tydings, MD | Children's National Hospital

Volumetric analysis provides a more detailed and meaningful approach to measuring treatment effect of targeted therapies for irregularly shaped desmoid tumors.

Claire Wunker, MD | Luenfeld-Tanenbaum Research Institute

Rhabdomyosarcoma requires new treatments to improve survival and decrease long term side effects. TLD with MRgHIFU is a promising treatment combination. We found higher doxorubicin levels in the tumor after 20 minutes of heating compared to controls in a murine RMS model.

Women's Health

Kimberly Anneveldt, MD | Isala Hospital

When implementing MR-HIFU treatment, a learning curve should be considered. After overcoming this curve however, MR-HIFU for uterine fibroids leads to clinically successful treatments.

Kimberly Anneveldt, MD | Isala Hospital

By performing a long-term randomized controlled trial comparing MR-HIFU with standard care, we will provide currently unavailable data about the proper place of MR-HIFU when it comes to uterine fibroid treatment.

Gil Dubernard, MD, PhD | Hospices Civils de Lyon, LabTAU

We report for the first time that transrectal HIFU therapy for rectosigmoid endometriosis is feasible. No major complication was observed after 20 procedures with a significant impact on gynecological and digestive symptoms.

Cardiovascular Disorders

Ethan Bendau, MS | Columbia University

Low-intensity focused ultrasound-mediated hyperthermia (<3.5°C) in the thalamus and hypothalamus of anesthetized mice results in modulation of autonomic regulatory function, including reversible modulation of heart rate and respiratory rate.

Elodie Cao, MD | NSERM

Cardiac arrhythmia treatment is challenging. HIFU therapy is a promising alternative method to induce full thickness transmural thermal lesions. Ex vivo experiments were conducted with a new transesophageal probe. Results demonstrated the ability to produce transmural lesions.

Jennifer Carrol, BVMS | Virginia Polytechnic Institute and State University

HIFU can be used for the treatment of canine subcutaneous solid tumors. It is feasible and generally safe, resulting in discrete regions of coagulative necrosis. Treatment results in a pro-inflammatory changes to the tumor microenvironment that may have an anti-tumor effect.

Wojciech Kwiecinski, PhD | Cardiawave

Non-Invasive ultrasound therapy generated by Valvosoft (Cardiawave, France) is feasible and safe in patients (n = 10) with severe aortic valve stenosis and can improve aortic valve area and hemodynamic parameters. Larger clinical studies need to be conducted.

Grace Lai, MD, PhD | The Hospital for Sick Children

We propose an optimal set of sonothrombolysis parameters for a 1MHz HIFU transducer through systematic testing of a range of cavitation parameters on in vitro porcine blood clots.

Hossein Mehrad, PhD | Islamic Azad University – Tabriz Branch

Ultrasound-mediated transfection therapy is a feasible and efficient method for improving vascular endothelial dysfunction.

Ralf Seip | SonaCare Medical, LLC

The usability of commercially available HIFU probes can likely be extended for applications in ultrasound image-guided ablation of venous malformations, significantly reducing the introduction time of this technology into clinical practice.

Pediatric Indications

Rohan Janwadkar | Florida Atlantic University
Charles E. Schmidt College of Medicine

Focused ultrasound therapy in pediatric patients provides a uniquely advantageous therapeutic platform with no radiation exposure and no incisions.

Narendra Sanghvi, MSEE | SonaCare Medical, LLC

Novel applications of LoFU (AKA-LIPUS, pHIFU) can help accelerate regeneration of the micro-vascular system by homing of stem cells.

Travis Tierney, MD, PhD | Imperial College London

Image-guided high-energy focused ultrasound is a method for introducing non-ionizing energy deep into the brain without a craniotomy and may be especially useful in a number of pediatric conditions where alternatives to conventional (open, endoscopic or laser) surgery are needed.

Veterinary Indications

Harshini Ashar | Oklahoma State University

FUS can be used for noninvasive treatment of spontaneously occurring canine cancers. FUS ablation of solid tumors can also enhance the local & systemic populations of anti-tumoral macrophages and activated T-cells to improve immunity against cancer.

Kyriakos Spanoudes, DVM | Cyprus University of Technology

A reliable MRgFUS system, compatible with multiple MR systems, will offer a solution for incisionless intervention for tumour ablation in veterinary hospitals. Its utilisation can be of therapeutic or palliative intent.

Technical

Abdul Kareem Ahmed, MD | Medical University of South Carolina

Unilateral MR-guided focused ultrasound thalamotomy has lower treatment requirements than unilateral pallidotomy. This reflects the treatment envelope of current systems. These findings can inform patient selection and treatment planning for new, peripheral cerebral targets.

Shaikhah Alkhadhr | The Pennsylvania State University

The numerical representation used to compose the acoustic properties of the skull in transcranial focused ultrasound (tFUS) has a direct impact on the resulting intracranial fields. These properties should be represented carefully to carry out meaningful tFUS simulations.

Irving C. Allen | Virginia Maryland College of Veterinary Medicine

These data support the feasibility of using the immunocompromised pig model for the design and evaluation of clinically relevant, novel medical devices to treat pancreatic cancer and beyond.

Steven P. Allen | University of Virginia

Experiments in a preclinical model demonstrate that MRI diffusion weighted imaging can detect thermal ablation in the thalamus within minutes after treatment.

Steven P. Allen | University of Virginia

We present a method for estimating and predicting the effects of magnetic field aberrations induced by focused ultrasound devices inside an MRI scanner.

Steven P. Allen | University of Virginia

Iron oxide nanoparticles promise to improve MR guidance during FUS. Prefocal cavitation remains a primary concern for nanoparticle design.

Simone Ambrogio, PhD | St. Thomas Hospital

Development of reliable MRgHIFU test objects may be crucial for training, R&D, device calibration, definition of exposure parameters for optimizing procedures, comparing results among different centers, and developing protocols for Quality Assurance.

Diana Andrés | Universitat Politècnica de Valencia

Acoustic holograms are a cost-effective solution for focusing ultrasound beams in the brain. They have demonstrated their capability to correct skull aberrations, and, simultaneously, to adapt the ultrasonic focus to the shape of complex bilateral deep brain structures.

Haim Azhari | Technion Institute of Technology

Elastography metrics may help improve treatment assessment of many MRgFUS therapies. In this work, feasibility of an elastography technique that leverages the use of conventional MRgFUS hardware was presented and demonstrated in phantom experiments.

Avinoam Bar-Zion | California Institute of Technology

Air-filled proteins allow genetically engineered tumor-homing bacteria and mammalian cells to be remotely detonated with ultrasound. Gas vesicle cavitation enables triggered payload release and propulsion and produces controlled damage to surrounding cells and tissue.

Hongchae Baek | Washington University in St. Louis

The mechanothermal effect of FUS was proven to have a higher success rate in evoking motor responses than mechanical effects alone. The mechanothermal mechanism warrants further investigation to improve the FUS neuromodulation technique.

Thomas Bancel | Physics for Medicine Paris - ESPCI

Computation time for transcranial HIFU brain surgery to assess phase shifts induced by the human skull can be reduced by an order of magnitude when simulations are performed at half the frequency (450kHz) of the transducer transmit frequency (900kHz).

Thomas Bancel | Physics for Medecine Paris – ESPCI

For central brain targets, the clinical manufacturer provided ray-tracing algorithm for transcranial aberration correction shows only a 2% loss in pressure compared to 3D finite-difference algorithms.

Alec Batts | Columbia University

Patient-specific simulation of transcranial acoustic wave propagation requires high-resolution CT scans with resolved trabecular microstructure to accurately predict acoustic beam distortion and signal attenuation.

Boris Breuer, MSc. | Eindhoven University of Technology

The raytracing approach by (Modena et al., 2018) can be used to simulate HIFU induced heat production and temperature profiles in fluids.

Samuele Cabras | Istituto Neurologico Carlo Besta

MRgFUS is a technique for creating thermal lesions within dysfunctional brain circuits. The aim of this study is to assess the stereotactic accuracy of VIM thalamotomy in a cohort of patients treated for tremor using Kranion, an open-source software.

Fant Cecile, DVM | INSERM

Pulsed cavitation ultrasound can potentiate anti-PD1 in a partially sensitive tumor model. The enhanced treatment efficacy is immune dependent, at least partially through a CD8+ T-cells mediated response, and potentially through an increased DC-mediated response.

Jin Woo Chang | Yonsei University College of Medicine

With the newly developed Auto-Focusing(AF) Echo imaging technique, MRgFUS was successfully performed for patients with low SDR, achieving a therapeutic temperature without any adverse effects.

Andrew Chen, BS | George Washington University

Autofluorescence imaging of ultrasound effects on the pancreas can provide information on metabolic activity. Thermal effects of ultrasound may counteract the upregulation of metabolic activity induced by mechanical effects.

Daria Chupova | Lomonosov Moscow State University

We demonstrate the theoretical feasibility of using a new class of fully populated multi-element phased arrays to achieve shockforming conditions at the focus and tight focusing through an intact skull over a wide 40 mm range of depths.

Sam Clinard | Focused Ultrasound Foundation

The FUS Foundation made available instructions and software to build and control a hydrophone scanning tank, using 3D printing and sourced parts, for a total cost of about \$1k. This low-cost 3D tank is an open-source alternative to commercial systems.

Christian Coviello, PhD | OxSonics Therapeutics

Penetration of drugs into and throughout solid tumors is recognized as a major limitation to their effectiveness. SonoTran is a drug agnostic solution requiring no reformulation. This work validates the preclinical safety and performance of the system leading to clinical trial.

Daniel Dahis, MSc | Technion Institute of Technology

The Golay coded sequences offer an opportunity to monitor FUS thermal brain treatments. These sequences can be implemented in the same FUS probe used for treatment. The obtained echo-shifts vs. temperature trajectories can serve as a tool for temperature estimation of the brain.

Andrew Drainville, PhD | INSERM

Parametric simulation studies were used to quantify the sensitivity of transcranial focalization to uncertainties in estimated skull acoustic properties. Errors in density and sound speed can translate into significant errors in focalization, whereas attenuation has less impact.

Phillip Durham | The University of North Carolina at Chapel Hill

Focused ultrasound therapy with phase-change contrast agents can temporarily disrupt tumor blood vessels, and this disruption can be visualized immediately following treatment via acoustic angiography.

Nikolas Evripidou | Cyprus University of Technology

We demonstrate a pre-clinical MRI-guided robotic device using focused ultrasound.

Nikolas Evripidou | Cyprus University of Technology

MRI guided positioning device using focused ultrasound for treatment of prostate cancer is described.

Marc Fournelle | Fraunhofer Institute for Biomedical Engineering

Acoustic back-propagation simulations can be used to determine patient-specific delay patterns that allow compensation for skullbone related sound field distortion. Matrix arrays or phase plates can be used to generate these specific delays.

Rezida Galimova, MD, PhD | Intelligent Neurosurgery Clinic

Despite COVID infection limitations, innovative digital technologies allow us to perform MRgFUS neurosurgical procedures remotely. Intelligent Neurosurgery Clinic experience shows that even difficult neurosurgical procedures can be launched remotely with good results.

Yekaterina Gilbo | University of Virginia

Skull heating is not currently measured during FUS brain surgery. MR T1 thermometry uses T1 mapping to measure skull temperature but requires long acquisitions. Here we demonstrate rapid volumetric thermometry by using a 3D spiral UTE sequence with variable density acceleration.

Samuel Groth | University of Cambridge

OptimUS is a fast Python-scriptable computational suite for modelling therapeutic ultrasound. OptimUS includes efficient implementations of modern integral equation and finite element methods, and is straightforward to use on a single workstation and in highly parallel settings.

Juanjuan Gu, PhD | North Carolina State University

We introduce mSOUND, a user-friendly toolbox for the simulation of acoustic wave propagation in heterogeneous media. It is developed to fill an unmet need for an accuracy-efficiency balanced solver for modeling medical ultrasound, especially HIFU.

Sijia Guo, PhD | University of Maryland School of Medicine

Effective heating can be achieved in the mesial temporal lobe by MRgFUS, and potential skull heating can be reduced by blocking certain transducer elements. Large volume lesions will require multiple sonication targets.

Edwin Heijman | University of Cologne, Philips Research Eindhoven

We propose a new measure, the Thermal Dose Performance Temperature (TDPT), to evaluate MR-HIFU hyperthermia treatments regardless of the set target temperature and treatment time. Clinical data of an MR-HIFU hyperthermia therapy was used to assess the TDPT.

Yoni Hertzberg, PhD | NINA Medical

A new method of real-time US imaging of a HIFU field is evolving. The method can be used safely during USgHIFU procedures to provide a live image of the treatment beam to the practitioner as well as focal point tracking and improvement in treatment efficacy and safety.

Lorne Hofstetter | University of Utah

Elastography metrics may help improve treatment assessment of many MRgFUS therapies. In this work, feasibility of an elastography technique that leverages the use of conventional MRgFUS hardware was presented and demonstrated in phantom experiments.

Xuandi Hou | The Hong Kong Polytechnic University

We developed an ultrasonic mechanogenetic tool to manipulate neuronal activity and signaling with excellent precision by introducing nano-materials.

Sam Howard, PhD | Onda Corporation

The combination of this scatterer-free phantom with the reflectance-type fiber-optic hydrophone is a promising tool for treatment planning and quality assurance for HIFU.

Ming-Yen Hsiao, MD, PhD | Duke University

Acoustic waves induce changes in calcium signaling and permeability change of an endothelial monolayer, possibly by acoustic streaming-induced shear stress. The system provides a useful platform for exploring the mechanical effect of US on BBB opening.

Zhongtao Hu, PhD | Washington University in St. Louis

This study demonstrated the feasibility of using a four-sensor network to transcranially locate cavitation sources in 3D. The proposed method has the unique advantages of being low-cost in manufacturing and low-cost in computation. Future studies are needed to improve accuracy.

Sumeeth Jonathan | Universitat Politècnica de Valencia

We demonstrate how a single-element transducer with a 3D-printed holographic lens allows (1) simultaneous production of bilateral BBB opening in anesthetized mice in vivo, and (2) compensation of the aberrations due to the skull and the water cone.

Sumeeth Jonathan, PhD | Vanderbilt University

A multi-voxel MR-ARFI-based autofocusing method is proposed for rapid aberration correction of MR-guided focused ultrasound acoustic pressure fields. We demonstrate that as few as two MR-ARFI acquisitions can be used to refocus a programmatically aberrated pressure field.

Minoo Kabir | Stanford University

We propose a novel technique for in-situ acoustic characterization of the skull based on acoustic microscopy. It is able to provide a full characterization including both longitudinal and shear velocities and attenuations.

Ki Chang Kang | Hanyang University

We propose and present the concept and feasibility of the dual-mode conversion technique using an array of wedge transducers, which is able to reduce skull heating, and extend the focal spot range.

Peter Kaczowski, PhD | Verasonics, Inc.

The new HIFUPlex PLUS™ 1000 and 3000 platforms from Verasonics and Sonic Concepts are turnkey commercial systems for preclinical research in focused ultrasound therapeutic applications. They enable typical experimental USgFUS preclinical workflows.

Woonbing Kang, BS | Jeju National University

Kranion software is a good tool for patient selection and validation of the treatment for thermal ablation.

Maria Eleni Karkatsani | Columbia University

Diffusion tensor imaging may be used in the clinic for detecting BBB opening following FUS treatment and/or to evaluate BBB integrity in brain-related pathologies.

Rajwinder Kaur | Ryerson University

Pulsed FUS was used successfully to induce primary injury to the nuclei of mouse brain endothelial cells. It was insufficient to directly deform the nuclei, but sufficient to irreversibly affect their integrity. Therefore, nuclei became more vulnerable to hypoxia—a well-known secondary process in TBI.

Vera Khokhlova | University of Washington

Mechanical ablation of tissue volumes with real-time ultrasound control of the degree of tissue liquefaction is feasible using boiling histotripsy (BH) technology combined with electronic focus steering and Doppler-type imaging.

Sait Kilinc | Georgia Institute of Technology

According to a figure of merit based on the ratio of ultrasound power transmission to maximum temperature rise in the skull, mode conversion in the skull does not provide an advantage for tFUS over normal or close to normal incidence.

Evgenii Kim | Korea Institute of Science and Technology

FUS was introduced as a noninvasive technique to modulate spinal cord activity. The results showed that FUS could temporarily suppress limb movement induced by electrical stimulation of the motor cortex, possibly opening new applications for FUS.

Jinwook Kim, PhD | The University of North Carolina at Chapel Hill

Nanodroplet-mediated pulsed focused ultrasound generates higher cavitation intensity compared to microbubble-induced cavitation or free-field cavitation. Cavitation enhanced sonothrombolysis by nanodroplets outperforms conventional HIFU or microbubble-assisted therapy.

Kisoo Kim, PhD | University of California, San Francisco

For volumetric hyperthermia treatments using the ExAblate body system, we investigated sector vortex beamforming methods as a sonication strategy for HT and developed an acoustic and biothermal simulation framework for rapid evaluation of the sector vortex approach.

Kisoo Kim, PhD | University of California, San Francisco

Motion-robust, multi-slice, real-time MR thermometry was developed to monitor ultrasound thermal therapy in abdominal organs. This all-in-one MR thermometry is available for accurate and stable temperature measurements in abdominal organs.

Young Hun Kim | Hanyang University

The skull's effect on the pattern interference radiation force created by focused transducers using the Fresnel lens was measured. By using two transducers with the same design, we measured the radiation force at the focal point without the skull.

Vibhor Krishna, MBBS, SM | OSU Wexner Medical Center

Thermal neuromodulation was observed in a minority of subthreshold sonications. Higher temperatures and bigger spot sizes were associated with thermal neuromodulation.

Elena Konnova | Lomonosov Moscow State University

The use of graphic accelerators in modeling nonlinear ultrasound beams speeds up simulations several times compared to those performed on central processors and makes such simulations feasible for practical implementation in HIFU using a personal computer.

Varsha Kumar | University of Michigan

Results from K-wave simulations that quantify the focal shift due to aberration reveal the need to perform real time corrections during each treatment. It is also critical the media surrounding the transducer better matches the speed of sound in skin.

Grace Lai, MD, PhD | The Hospital for Sick Children

We propose an optimal set of sonothrombolysis parameters for a 1MHz HIFU transducer through systematic testing of a range of cavitation parameters on in vitro porcine blood clots.

Hohyun Lee | Georgia Institute of Technology

To address the possible downsides of MRI-guided FUS systems, we developed and evaluated an US-guided FUS system for BBB opening and targeted drug delivery in central nervous system with sub-millimeter accuracy. The system is also capable of real time closed-loop control using PCD.

Jooho Lee, MS | Jeju National University

A carbon nanotube transducer can be used for the application of therapeutic ultrasound by increasing the negative pressure of the shock wave.

Steve Leung | Stanford University

MR-simulated-CT images are a promising alternative to CT images for treatment planning of transcranial focused ultrasound.

Kiaoyue Li, MS | Columbia University

We show that Harmonic Motion Imaging (HMI) can be used to monitor Focused Ultrasound Surgery (FUS) ablation in mammary breast tumors in mice using simultaneous 2D imaging for the first time.

Defei Liao | Duke University

The optimal pulse length of US for activating Piezo1 in HEK293t cells under 60 s total treatment time and at 20% duty cycle is 20 ms. Fine-tuning the PL of US may significantly improve the efficacy and safety of sonogenetic applications.

Xilun Liu, MS | Pennsylvania State University

In this study, to create and control tumor ablation, we propose combining CGM, SGC using the adjoint method. Our results show that our proposed method is computationally more efficient than the SGC method.

Asis Lopez, PhD | U.S. Food and Drug Administration

The outcomes of these in vivo experiments are expected to assist in predicting the rupture probability for HIFU + Microbubble procedures.

Ning Lu | University of Michigan

The feasibility of transcranial histotripsy has been demonstrated in the in vivo pig brain. No excessive hemorrhage or edema occurred post-treatment.

Michael Malmberg | University of Utah

Fast T1 mapping is needed for simultaneous proton resonance frequency/T1 thermometry. A T2 correction was applied via simulation to a single reference variable flip angle method of T1 mapping that can eliminate the calculation's bias, showing potential viability of fast, accurate T1 thermometry.*

McKenzie McLean | University of Utah

Errors in proton resonance frequency thermometry can occur when fatty tissues are heated. A correction method using T1 times to estimate temperature change is proposed and evaluated, demonstrating that this correction may improve MR thermometry results during MRgFUS treatment.

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

Our method to estimate the accumulated thermal dose predicted the shape of the resulting lesions segmented 24 h after treatment. The device software's 17 CEM43 threshold matched well on average with lesions segmented 24 h after treatment.

Nathan McDannold | Brigham and Women's Hospital, Harvard Medical School

This approach can visualize anatomic landmarks that are useful in refining atlas-based targeting for MRgFUS. Since the same data is used for MRTI and anatomic visualization, there are no errors induced by registration errors or image distortion, and no extra time is needed.

Chitra Meduri, MS | Virginia Polytechnic Institute and State University

We designed a custom, image-guided FUS system to identify and characterize FUS regimes capable of producing a range of mechanical, thermal, or combined mechanical-thermal effects in mouse Achilles tendons in vivo, enabling us to study effects of FUS on tendon healing.

Robb Merrill, MS | University of Utah

A conformable, convective skin-cooling device that can be integrated with existing MRgFUS systems to effectively prevent skin burns and reduce lengthy treatment times is presented. Superficial targets were treated without causing skin burns during ablative in vivo large animal model studies.

Kaylee Meyers | Michigan Technological University

To accelerate repair in tendon tissue, our group has developed an injectable adhesive hydrogel containing fibrin x-particles with the capacity for thermal and mechanical controlled release of nitric oxide, an antimicrobial signaling molecule that influences ECM turnover, via FUS.

Ali Mohammadabadi, PhD | University of Maryland School of Medicine

Pulsed focused ultrasound nondestructively reduced interstitial fluid pressure in solid tumors, increasing penetration and overall delivery of nanoparticle probes. These results support our therapeutic studies and may facilitate future clinical translation for cancer treatment.

Anirudh Natarajan | University of California, Berkeley

Automated post-processing of imaging data will rapidly speed up and simplify analysis allowing researchers to focus on optimizing their experimental preparations. Creating an analysis pipeline in Python will also capitalize on the most current image analysis algorithms.

Kota Ono | Tokyo University of Pharmacy and Life Sciences

By loading miRNA on nanobubbles coated with cationic polysaccharides, efficient miRNA delivery after systemic injection is possible using ultrasound.

Frederic Padilla | Focused Ultrasound Foundation

Contrast enhanced US (CEUS) intraoperative images can be quantified for accurate analysis of microbubble distribution in the human brain, allowing discernment between brain tissues and tumor types. Such quantitative imaging will have implications for MB-based imaging and treatments.

Ki Joo Pakh, PhD | Korea Institute of Science and Technology

In addition to boiling histotripsy, this proposed pressure-modulated shockwave histotripsy method could be employed for precise tissue fractionation and tissue decellularisation.

Thomas Payen, PhD | INSERM

Higher performance in lesion monitoring is needed for widespread use of focal HIFU treatments in prostate cancer. Passive elastography can be modified to provide stiffness maps using slow-rate B-mode images acquired on a conventional clinical ultrasound systems which can be used to guide treatment.

Chenguang Peng | Brigham and Women's Hospital

We tested phase change nanoemulsions for facilitating transcranial ablation of healthy and tumor tissues. The results suggest that nanoemulsion-mediated ablation can provide better spatial control of lesion formation and destroy a larger fraction of tumor compared to microbubble-mediated ablation.

Antonios Pouliopoulos, PhD | Columbia University

Neuronavigation-guided FUS allows bedside brain treatments without the need of on-line MRI guidance and with minimal focal distortions or skull heating. Additionally, clinically-relevant FUS-mediated BBB opening may lead to a reversible immune response and cognitive improvement.

Richard Price, PhD | University of Virginia

Through computational simulation of the glymphatic system, we demonstrate that augmentation of perivascular spaces during FUS-induced blood-brain barrier opening is predicted to increase solute clearance.

Richard Price, PhD | University of Virginia

We develop a Boolean logic-based model for brain endothelial cell signaling which we use to predict how transcriptomic changes, resulting from FUS treatment of the brain, could impact BBB integrity.

Jade Robert | INSERM

Electromechanical wave imaging (EWI) could provide mapping of cardiac activation. EWI feasibility was assessed in-vivo on two swines using an intracardiac probe. EWI acquisitions depicted the source of cardiac activation consistent with the pacing site in the RVOT region.

Fareeha Safir | Stanford University

We designed an acoustic droplet ejection technique operating at 150 MHz that rapidly splits a blood sample into single-cell droplets using focused ultrasonic waves. When coupled with spectroscopy and a convolutional neural net, it allows for culture-free bacterial bloodstream diagnosis.

Malia Sanghvi | Sonacare Medical

Lung tissue can be imaged by ultrasound technology. It responds to therapeutic ultrasound and cavitation can be sustained at very low power levels. There is potential for focused ultrasound application in lung tissue.

Narendra Sanghvi, MSEE | SonaCare Medical, LLC

Novel applications of LoFU (AKA-LIPUS, pHIFU) can help accelerate regeneration of the micro-vascular system by homing of stem cells.

George Schade, MD | University of Washington, Department of Urology

Transrectal boiling histotripsy (BH) of the prostate is feasible with a pre-clinical device. Both canine and human tissue are susceptible to BH, though human tissue may be more resistant. Future studies will examine treatment optimization and resistance mechanisms.

Shirshak Shrestha | University of Calgary

Low-frequency imaging can be used to estimate the characteristics of layered material with mm-sized precision. These properties can be used to correct the skull aberrations for targeting brain regions, enabling precise targeting of ultrasound for neurostimulation studies.

Emma Slominski | University of Utah

We show that the method of phase correction for improving the focus for neurological treatment depends on the method used to obtain phase correction value.

Norman M. Spivak | University of California, Los Angeles

Ex-vivo sonication of brain tissue does not induce histologic damage until intensity levels are above 25 W/cm². Sonication below this value is likely safe, but further safety testing is needed.

Janina Strobel | University of Cologne

Larger multicenter trials with different MR-HIFU systems require standardized treatment protocols to achieve reliable results. To address this issue we developed a reusable bone phantom for comparison of different MR-HIFU treatment protocols.

Ivan M. Suarez Castellanos, PhD | INSERM

Focused Ultrasound is capable of stimulating field Post-Synaptic Potentials (fEPSPs) from neural structures of hippocampal brain slices. As opposed to electrical stimulation, fEPSPs can be stimulated across the entire hippocampus within the region targeted by the focal spot.

Jonathan Sukovich, PhD | University of Michigan

A system for controlling transmit-receive capable histotripsy array elements on a per-channel basis is described. Its capabilities for localizing cavitation events and assessing induced tissue damage transcranially using the received acoustic signals are demonstrated.

Sean Taffler, D.Phil. | Acoustiic Inc.

Acoustiic presents a therapy system that leverages emission plane electronics that allow the construction of arrays with up to 20w/cm² emission power, generating ultra dense widefield HIFU arrays that are usable within an MR system.

Caitlin Tydings, MD | Children's National Hospital

Volumetric analysis provides a more detailed and meaningful approach to measuring treatment effect of targeted therapies for irregularly shaped desmoid tumors.

Diya Wang, PhD | University of California, San Francisco

This study investigates a new clinical breast exam imaging approach for real-time monitoring of thermal processes and to assess the ablation area with high contrast.

Beat Werner, MSc | University Children's Hospital Zurich

Dedicated FUS system carrying a central ultrasound imaging probe, and a suitably positioned, acoustically transparent cranial substitute serving as an acoustic keyhole, might enable ultrasound-guided, frameless interventions for opening the BBB in deep-lying brain tumors.

Quanxiang Xian, PhD Candidate | Hong Kong Polytechnic University

This paper explores targeted surface and deeper brain stimulation by non-invasive ultrasound.

Xinquiang Yan, PhD | Vanderbilt University Medical Center

This work proposes a simpler solution that alleviates the curved dark band problem in brain images of the FDA-approved Insightec tcMRgFUS system, involving placing a passive reflecting antenna or resonator above the patient's head, with a "propeller-beanie" crossed-wire shape.

Dezhuang Ye, PhD Candidate | Washington University in St. Louis

This study found FUS + intranasal drug delivery efficiency depends on several key experimental parameters, including the time delay between intranasal administration & FUS sonication, the FUS pressure, and the waiting time to sacrifice the mouse post-FUS.

Jiejun Zhu | The Hong Kong Polytechnic University

Ultrasound neuron modulation is mediated by piezo1 in vitro. This result also suggests a possible mechanism for in vivo modulation. By controlling the expression of piezo1 we may be able to target specific neuronal pathways or nuclei for study in both basic and clinical neurosciences.

Lifei Zhu | Washington University St. Louis

MRgHIFU-induced large-volume (tROI diameter of 58 mm) hyperthermia is feasible in both deep and superficial targets achieving satisfactory temperature characteristics. Feedback control could be used to tailor the thermal dose distribution to critical structures.

Blake Zimmerman | University of Utah

Non-contrast enhanced multiparametric MR biomarkers outperform contrast-enhanced based nonviable tissue predictions for assessing MRgFUS procedures. Non-contrast assessment of MRgFUS procedures may potentially lead to more efficacious and safer MRgFUS treatments.

Miscellaneous

Abdul Kareem Ahmed, MD | University of Maryland School of Medicine

MR-guided focused ultrasound thalamotomy of the central lateral nucleus is feasible and results in a sustained clinical response one year after treatment for neuropathic pain. Patients often experience a reduction in their analgesic use, and improvement in pain symptoms.

Harshini Ashar | Oklahoma State University

A combination of FUS heating with antibiotic-laden thermally-sensitive liposomes can achieve high microbicide concentrations locally to induce clearance of bone infections, obviating the need for long-duration antimicrobial therapies and surgeries.

Bashar Badran, PhD | Medical University of South Carolina

Transcranial focused ultrasound (tFUS) is a promising, noninvasive, and focal method of stimulating deep in the brain. tFUS to stimulate the anterior thalamus produced antinociceptive effects on heat pain threshold. Further tFUS investigation is warranted.

Torsten Bove | TOOSonix A/S

This study presents a new 20 MHz HIFU system for clinical dermatology. Treatments were applied successfully to actinic keratosis, basal cell carcinoma and Kaposi's sarcoma. Results demonstrate close to 100% efficacy, low treatment time, and reduced pain level for patients.

Scott Burks, PhD | National Institute of Health

Mechanical forces from non-ablative pulsed focused ultrasound to different tumor cell types induce cytosolic Ca²⁺ transients that cause mitochondrial formation of superoxide and H₂O₂ which leads to double-stranded DNA breaks without apoptosis.

Scott Burks, PhD | National Institute of Health

Nonablative pulsed focused ultrasound initiates complex cellular calcium dynamics to induce NFκB, which is a major mediator of bioeffects necessary for ultrasound-induced stem cell homing.

Parwathy Chandram, PhD | National Institute of Health

This study demonstrates the immunomodulatory potential of non-ablative pulsed focused ultrasound in altering an antiinflammatory, tumor microenvironment towards a pro-inflammatory, anti-tumor landscape by engaging both innate and adaptive arms of immunity.

Chris Childers, MD Candidate | Virginia Polytechnic Institute and State University Carillion School of Medicine

Histotripsy is a promising novel technology for prophylaxis or treatment of catheter-associated urinary tract infections. Initial data support the need for future work in treating medical device related biofilms with histotripsy.

Gadi Cohen | National Institute of Health

Temporal alterations of non-ablative pulsed focused ultrasound exposure display a pro-inflammatory proteomic profile within the tumor microenvironment, thus underscoring the potential use of pFUS as neoadjuvant treatment approaches in cancer immunotherapy.

Grace Lai, MD, PhD | The Hospital for Sick Children

HIFU sonothrombolysis in an in vivo porcine intraventricular hemorrhage model can result in far field effects due to air in nasal sinuses and near field effects at higher powers but can be safe and effective given proper precautions.

Jami Mata, MS, PhD | University of Virginia

Non-invasive ablation and debulking of lung tumors seems possible with the novel method proposed using MRgFUS. We successfully ablated lung tissue deep in the lung without incisions, reducing the risk for infection and other complications.

Ali Mohammadabadi, PhD | University of California, Los Angeles

Pulsed focused ultrasound nondestructively reduced interstitial fluid pressure in solid tumors, increasing penetration and overall delivery of nanoparticle probes. These results support our therapeutic studies and may facilitate future clinical translation for cancer treatment.

Martin Monti | University of California, Los Angeles

Thalamic Low Intensity Focused Ultrasound Pulsation might provide for a safe and potentially effective approach to enhancing behavioral responsiveness in vegetative state and minimally conscious state patients, a cohort for whom there is virtually no treatment available.

Malia Sanghvi | SonaCare Medical, LLC

Lung tissue can be imaged by ultrasound technology. It responds to therapeutic ultrasound and cavitation can be sustained at very low power levels. There is potential for focused ultrasound application in lung tissue.

Narendra Sanghvi, MSEE | SonaCare Medical, LLC

Neuronavigation-guided focused ultrasound can effectively enhance the delivery of chemotherapeutic agents and improve tumor control.

Ralf Seip | SonaCare Medical, LLC

The usability of commercially available HIFU probes can likely be extended for applications in ultrasound image-guided ablation of venous malformations, significantly reducing the introduction time of this technology into clinical practice.

Marie-Hélène Tomé | Albert Einstein College of Medicine

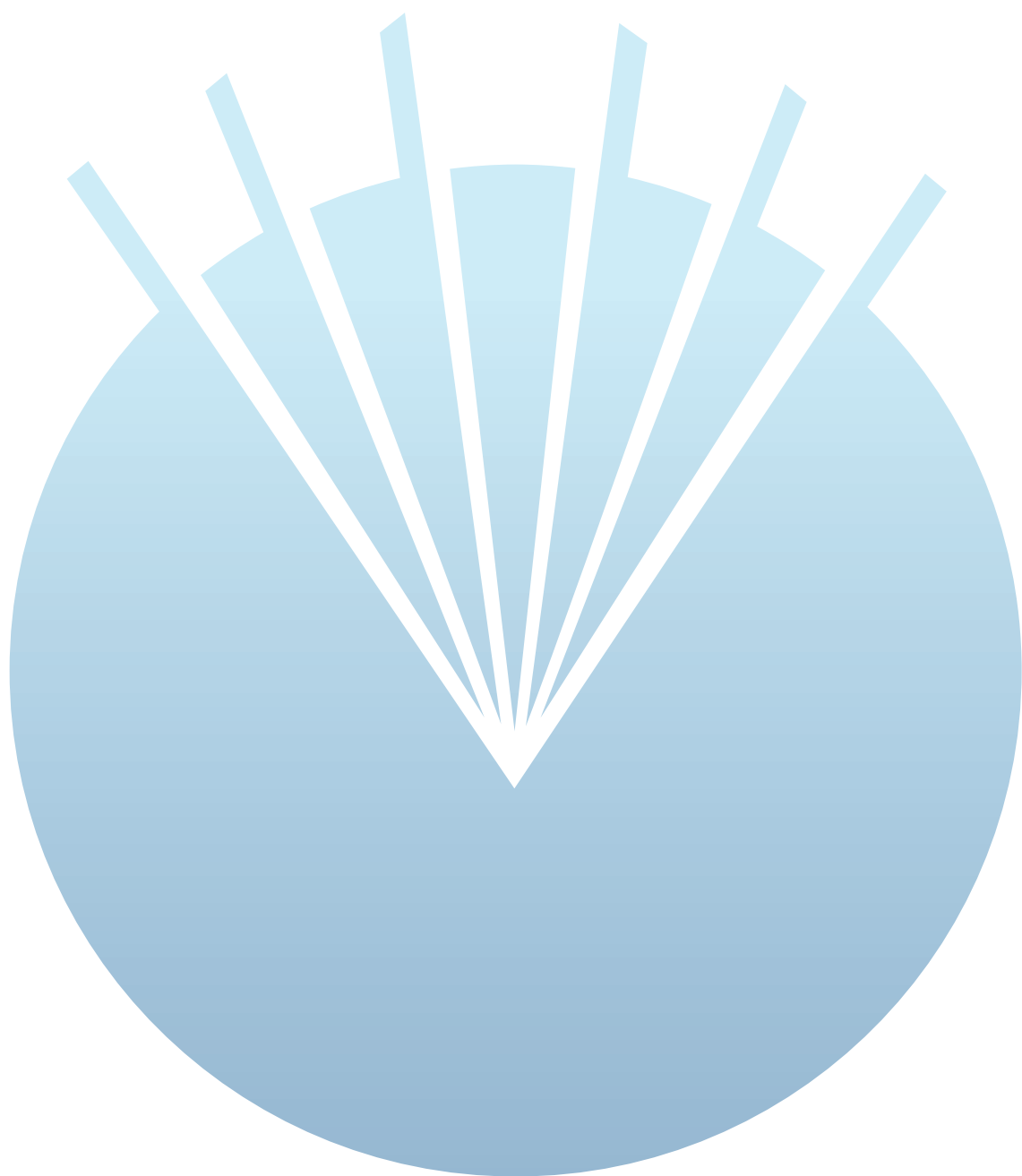
Chemical disruption of the cytoskeleton alters cell shape, disorients cells, and inhibits their ability to move directionally. LOFU could have similar effects thereby modulating cellular metastatic potential through interference with cytoskeletal elements.

Yak-Nam Wang | University of Washington

Focused ultrasound, specifically histotripsy, may be a viable technology for in situ treatment of acoustically accessible abscesses, obviating the need for percutaneous drainage. Focused ultrasound, specifically histotripsy, may be a viable technology for in situ treatment of acoustically accessible abscesses, obviating the need for percutaneous drainage.

Frank Wolfram, PhD | SRH Wald-Clinic

One Lung Flooding (OLF) for Lung FUS can be performed safely in supine, lateral left & right position. The use of superimposed Jet ventilation during OLF enables continuous ventilation whilst reducing motion to an extent that no motion compensation of intrapulmonary targets is needed.





FOCUSED
ULTRASOUND
FOUNDATION

1230 Cedars Court, Suite 206
Charlottesville, VA 22903, USA

+1 434.220.4993
fusfoundation.org

