

8th International Symposium on **Focused Ultrasound**

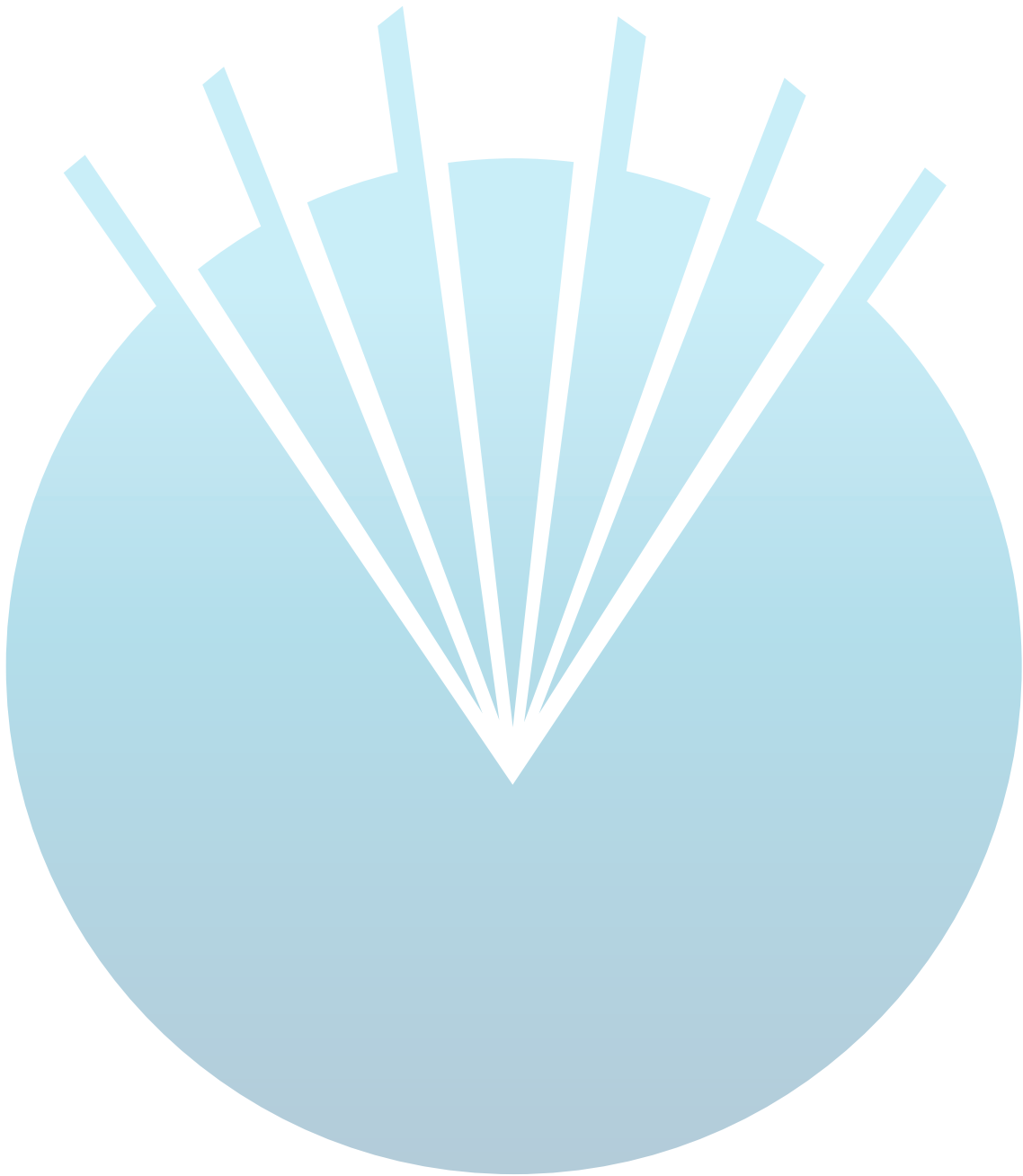


October 23–27, 2022

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



FOCUSED
ULTRASOUND
FOUNDATION



Contents

Sunday, October 23, 2022

- 6 2022 Awards Ceremony
 - 6 Clinical Adoption Award
 - 7 Lifetime Achievement Award
 - 8 Visionary Award
 - 10 Commercialization Pathfinder Award
 - 12 Ferenc Jolesz Memorial Award
 - 13 Andrew J. Lockhart Focused Ultrasound and
Immuno-Oncology Postdoctoral Fellowship
 - 14 Young Investigator Award Recipients
 - 19 Global Intern Award
 - 19 Bracco Women in Focused Ultrasound Award

.....

Monday, October 24, 2022

- 22 Welcome
- 23 Honorary President's Address
- 25 Movement Disorders Tremor
Essential and PD
- 28 Movement Disorders: Parkinson's Disease
Dyskinesia/Motor/Dementia
- 31 Neurodegenerative Diseases—Alzheimer's
- 34 Keynote Speaker
Geoff Martha, CEO, Medtronic
- 35 Epilepsy
- 37 Psychiatric Disorders
- 40 Why Advocacy?
- 43 Trials and Tribulations of Startups

.....

Tuesday, October 25, 2022

- 48 **Brain Tumors—Glioblastoma**
- 52 **DIPG**
- 56 **Keynote Speaker**
Bob Smith, *Senior Vice President, Global Gene Therapy Business, Pfizer*
- 58 **Liquid Biopsy for Brain Tumors**
- 63 **Sonodynamic Therapy**
- 68 **Chronic Pain**
- 74 **Veterinary**
- 77 **FDA Town Hall**
- 81 **Capital Markets Fireside Chat**

.....

Wednesday, October 26, 2022

- 88 **Cancer Immunotherapy—Where are we now?**
- 92 **Cancer Immunotherapy—Looking to the future**
- 97 **Machine Learning and FUS**
- 101 **Brain Imaging Guidance, Targeting, and Monitoring**
- 106 **Gynecologic Indications**
- 110 **Technology Breakthroughs**
- 114 **Technology Gaps**
How can technology breakthroughs lead to broader adoption?
- 120 **Special Lecture**
Reimbursement Through the Eyes of CMS
Thomas Scully, *Former Administrator of the Centers for Medicare and Medicaid Services*
- 122 **Special Lecture**
Evidence Development for Medical Devices
Jill Hagenkord, *Chief Medical Officer, Optum Genomics*
- 124 **Overview on the Status of Reimbursement**
Michael Broad, *Data Strategy Director, Focused Ultrasound Foundation*
- 126 **Cost of Care Calculator**
Mark Carol, *Senior Consultant, Focused Ultrasound Foundation*
- 128 **Fireside Chat on Regulatory Strategies**

.....

Thursday, October 27, 2022

- 132 **Special Lecture**
FUS for Thyroid
Brian Lang, *University of Hong Kong*
- 134 **Special Lecture**
FUS for Diabetes
Chris Puleo, *GE Global Research*
- 136 **Pancreatic Cancer**
- 140 **Back Pain**
- 145 **Soft Tissue Tumors**
- 149 **Liver**
- 152 **Prostate**
- 157 **Registry Panel**
- 160 **Special Lecture**
Addressing Disparities in Clinical Trials
Freda Lewis-Hall
- 161 **Gene and Cell Therapies**
- 164 **Closing Remarks**

.....

Sunday, October 23, 2022



Sunday,
October 23, 2022

2022 Awards Ceremony

Clinical Adoption Award

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



Zhibiao Wang, MD

Chairman
Chongqing Haifu Medical
Technology CO LTD



View on the Foundation's
[YouTube channel](#) >

Zhibiao Wang, MD, was honored with the foundation's inaugural Clinical Adoption Award. In 1999, Prof. Wang founded Chongqing Medical Focused Ultrasound Technology Development Co., Ltd. (later renamed Chongqing Haifu Medical Technology Co. Ltd.) and now serves as the chairman. He leads the company's research in the fields of device development, clinical application, and marketing. Prof. Wang developed the company's, and China's, first high-intensity FUS therapeutic system that is used to treat malignant tumors (e.g., liver cancer, pancreatic cancer, breast cancer, osteosarcoma, soft tissues sarcoma) and a wide range of benign diseases, such as uterine fibroids and adenomyosis. The Chongqing Haifu device has been exported to 28 countries and regions and has collectively treated more than 200,000 patients with benign and malignant tumors worldwide. The company has since developed a series of FUS therapeutic devices to treat nontumor diseases, such as diseases of the vulva surface and cervix, osteoarthritis, allergic rhinitis, soft tissue injury, pain, and more.

Prof. Wang's career in therapeutic ultrasound has spanned 34 years. He has made pioneering contributions to the field of ultrasound therapy, including breakthroughs in basic research, large medical equipment development, clinical applications, and industry standards. He is a Professor of Medicine and leads the State Key Laboratory of Ultrasound in Medicine and Engineering at Chongqing Medical University in China. His contributions to therapeutic ultrasound research have garnered major funding grants and second prize in both the National Technology Invention Award and the National Science and Technology Progress Award. He has published more than 50 scientific papers in leading journals of the field of ultrasound medicine. Prof. Wang earned his MD from Chongqing Medical University and has been practicing as an ob-gyn specialist.

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

Prof. Wang was unable to attend the symposium in person, but he sent in a lively, 5-minute video acceptance speech, where he thanked the foundation for the honor and described his motivations for developing FUS as a uterus-sparing treatment for gynecologic diseases, the work that he and his team have done to make Chongqing HAIFU the global leader in FUS treatments, and the ever-expanding list of indications that can be treated while minimizing harm to patients. Prof. Wang praised his research and clinical teams for their innovative pursuits and humanistic compassion and thanked the many patients who, by trusting their care to the FUS teams, have propelled and will propel the development of the technology as a powerful therapeutic option.

.....

Lifetime Achievement Award

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



Yoav Medan, PhD
*Former Vice President
and Chief Systems Architect
Insightec*

Yoav Medan, PhD, was posthumously presented with the inaugural Lifetime Achievement Award. He was informed of the award before he passed away in April 2022. Dr. Medan is among the elite pioneers of FUS therapy, dedicating more than 23 years to advancing the field. In 1999, Dr. Medan joined device manufacturer Insightec and served as Vice President and Chief Systems Architect for more than a decade. During his tenure at Insightec, Dr. Medan designed and implemented a robotic system, defined the software of the treatment systems to expand its capabilities for innovative early research, managed the engineering effort of the brain preclinical system, and implemented a fast method for ensuring the safe and correct output of installed FUS treatment devices. In addition, he supported luminary research sites in demonstrating future applications on the Insightec platform, such as treating a moving liver with real-time target tracking and thermometry and demonstrating neural modulation in mice.

Dr. Medan was a member of the foundation's Scientific Advisory Board and was influential in developing the technology behind FUSMobile, an FUS company addressing low back pain. In 2011, Dr. Medan's inspirational TEDMED presentation introduced FUS to countless individuals and inspired researchers to explore the technology. The video has been viewed more than 870,000 times. He received his PhD from the Technion-Israel Institute of Technology in 1984 and a Business Administration diploma from the University of Bradford in 1995.

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

At the symposium, Eyal Zadicario, PhD, Insightec's chief operating officer, accepted the award on behalf of Dr. Medan's family. He shared additional information about Dr. Medan's passion for helping others in his community, including co-founding a nonprofit for people who suffer from speech disorders. The Medan family thanked the foundation for honoring Yoav by sending a touching video tribute to his life and work.

.....

Visionary Award

The Visionary Award recognizes an individual who has created a larger vision for the future of FUS, and whose effort, passion, and persistence have been crucial to advancing the field. Previous Visionary Award recipients have included Lawrence Crum, PhD (2020), Narendra Sanghvi, PhD (2018), Kullervo Hynynen, PhD (2016), and Motti Zisser (2014).



Gail ter Haar, PhD
Institute for Cancer Research

Gail ter Haar, PhD, a renowned expert in the intersection of FUS and physics, was selected for the foundation's 2022 Visionary Award. Prof. ter Haar leads the therapeutic ultrasound team at the Institute for Cancer Research (ICR), where her work centers on understanding how ultrasound interacts with tissue. Her most recent research has involved developing devices and protocols for ultrasound-based treatments of cancer, investigating FUS for immune stimulation, and using FUS to treat liver and kidney tumors. In 2014, her team at ICR, along with colleagues at the Royal Marsden Hospital, were recognized as a Focused Ultrasound Center of Excellence. The group has completed FUS clinical trials for gynecological tumors and bone pain. Currently, her team is involved in a foundation-funded trial using FUS to resolve twin-twin transfusion syndrome.

Prof. ter Haar is the founding president of the International Society for Therapeutic Ultrasound (ISTU). She is also an honorary member of the British Medical Ultrasound Society and the Society of Thermal Medicine, honorary fellow of the American Institute for Ultrasound in Medicine, and fellow of both the Acoustical Society of America and the Institute of Physics and Engineering in Medicine. She leads the U.K.-based ThUNDDAR (Therapy Ultrasound Network for Drug Delivery and Ablation Research) network, which promotes collaboration between British and other European groups working with therapeutic ultrasound. Prof. ter Haar is deputy editor of *Ultrasound in Medicine and Biology*, associate editor of *Ultrasonics*, and on the editorial boards of the *International Journal of Hyperthermia* and *Medical Physics*. She has written 5 books, 32 book chapters, and more than 250 peer-reviewed research papers.

"Gail's contributions to the field of focused ultrasound are truly immeasurable," said Dr. Kassell. "She has led pioneering basic science and translational research that has ultimately impacted many patient lives. Additionally, her dedication to fostering collaboration among researchers—and creating a means to do so by establishing ISTU—has helped galvanize the focused ultrasound community."

"I was drawn to ultrasound because of its versatility," recalled Prof. ter Haar. "There is no other form of energy that cannot only be used to form sophisticated images and stimulate beneficial functional responses in tissue, but also be used to ablate localized targets, all noninvasively. It has been a privilege to be able to work in this field, which requires an understanding of thermal and mechanical effects, and to help develop techniques that have a very real impact on patients' lives."

Prof. ter Haar studied physics at Oxford University and received her master's degree in medical physics from Aberdeen University. She earned her PhD in physics at Guy's Hospital and holds a DSc in clinical medicine from Oxford.

At the symposium, Prof. ter Haar accepted the award and presented a brief overview of her career path in physics and ultrasound. She decided to learn about the bioeffects of ultrasound during her doctoral studies, and after completing her PhD, she joined ICR to use ultrasound to treat cancer. Throughout her career as a basic scientist, Prof. ter Haar advanced the use of FUS for hyperthermia, contributed to device development, and conducted many mechanistic and calibration studies. Clinically, Prof. ter Haar helped develop imaging guidance systems for oncology clinical trials and recently helped pioneer clinical studies for patients with twin-twin transfusion syndrome. “We need to choose what we do and do it well rather than trying to do everything,” she said. Beyond her scientific work, Prof. ter Haar spends time painting as a hobby and illustrated her slides with original paintings. She concluded her remarks by sharing her vision for what might be possible in the future of the field. She encouraged symposium attendees to focus on early-stage clinical funding, harness the versatility of bubbles in combination with FUS, continue to develop all combination therapies (e.g., FUS plus immunotherapies, viral therapies, radiotherapy, and nuclear medicine), create uniform treatment reporting methods, interact with unrelated scientific fields, and expand the already well-developed network of collaborations in the FUS community. Her future wish is for the increased scientific and clinical credibility that will make therapeutic ultrasound available to all who can benefit from it.

.....

Commercialization Pathfinder Award

The Commercialization Pathfinder Award recognizes an individual who has served as a galvanizing force in facilitating the rapid acceleration of FUS, speeding the transition from laboratory research to widespread adoption and utilization of the technology.

The recipient is always working to achieve the ultimate goal of using FUS technology to decrease death, disability, and suffering for patients with serious medical disorders around the world.



Jacob “Kobi” Vortman, PhD

*Former Vice President and
Chief Systems Architect
Insightec*

Jacob “Kobi” Vortman, PhD, founder and vice chairman of the board at Insightec, was presented with the inaugural Commercialization Pathfinder Award. Over his more than 23-year career in FUS, Dr. Vortman has shown an unrivaled dedication to the mission of improving lives with this revolutionary technology. Dr. Vortman’s career in FUS began as president of Elbit Medical Imaging, where he was responsible for developing the company’s proprietary MR-guided FUS (MRgFUS) technology. It was this technology that launched Insightec in 1999 as part of a joint effort by Elbit and GE Healthcare.

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

Dr. Zadicario, who joined Insightec when it was founded in 1999, worked alongside Dr. Vortman during his tenure. “Kobi has focused his and the team’s efforts on transforming focused ultrasound from a vision into a reality,” said Dr. Zadicario. “His extraordinary journey—realizing the potential, founding Insightec, overcoming unprecedented scientific challenges, and guiding the company through clinical evidence approval and acceptance—has positioned the technology at the leading edge of neurosurgery. He is an example to us all for the passion, dedication, and professionalism it takes to make breakthroughs happen.”

Professor Wladyslaw “Wady” Gedroyc, MBBS, MRCP, FRCR, a consultant radiologist at St. Mary’s Hospital, Imperial College NHS Trust, remembers Dr. Vortman’s galvanizing force in the early days of FUS. “He is not only a highly effective leader within Insightec, but he is a dedicated engineer and scientist,” said Prof. Gedroyc. “We met at what I believe was the very first focused ultrasound workshop, attended by only the handful of researchers in the area at that time. I had the idea that focused ultrasound would be a good treatment for uterine fibroids, and that is how our relationship began. I’ve always regarded him as a friend, first and foremost, and as a collaborator second, and only then third as a manufacturer.”

Another longtime friend and colleague, Dr. Kassell, has immense respect for Dr. Vortman's contributions to the field and his support of the foundation. Dr. Kassell called Dr. Vortman, "the perfect friend and the perfect colleague," and added that he is a true pioneer who has taken a vision and turned it into a reality through hard work, risk-taking, and innovation. "There is no individual who has done more to advance focused ultrasound from an idea to a full-fledged product that can improve the lives of countless patients as a new standard of care," said Dr. Kassell. "We are pleased to recognize his contributions with this award."

Over the last 23 years, Dr. Vortman contributed to 18 approved patents and 13 patent applications that are currently in different stages of prosecution. He received his PhD in Electro Optics and a BSc in Electrical Engineering from the Technion-Israel Institute of Technology, in Haifa. He also received a BSc in Physics and Mathematics from the Hebrew University of Jerusalem.

Dr. Zadicario accepted the award on behalf of Dr. Vortman, who was unable to attend, but sent an acceptance video in which he thanked the researchers who worked diligently to make the impossible possible. He said that Insightec is truly changing the lives of patients and their families for the better. With more than 30,000 patients already treated globally, the technology will help many more people in need for years to come. He thanked his partners at Insightec, the foundation, and the worldwide academic clinical teams for being a part of creating the amazing technology that is FUS. The goal has always been to make the world a better place and to help people. Dr. Zadicario said that the award highlights how Dr. Vortman realized the enormous scientific effort that was needed to commercialize a new technology and then turned that vision into a successful company that has positively impacted thousands of patients around the world.

.....

Ferenc Jolesz Memorial Award

The Ferenc Jolesz Memorial Award has a two-fold purpose: To honor the memory of Ferenc Jolesz, a world-class visionary whose passion for turning image-guided surgery from a vision to a reality of the 21st century and a pioneer of FUS as a noninvasive therapy; and to recognize and encourage this same innovative spirit in midcareer researchers and clinicians who continue to advance FUS. This award is supported by Insightec. Previous award recipients included Nir Lipsman, MD, PhD (2020), Seung-Schik Yoo, PhD, MBA (2018), and Nathan McDannold, PhD (2016).



Graeme Woodworth, MD

*Professor and chair of neurosurgery
University of Maryland
School of Medicine*

Graeme Woodworth, MD, professor and chair of neurosurgery at the University of Maryland School of Medicine, is the recipient of the 2022 Ferenc Jolesz Memorial Award. Dr. Woodworth's research focuses on improving treatments for malignant brain tumors, including the deadliest adult primary brain tumor, glioblastoma (GBM). He is investigating the use of FUS to open the blood-brain barrier (FUS-BBBO) to enhance drug delivery to brain-invading tumor cells, the major source of GBM recurrence. His team completed the first clinical trial of FUS-BBBO in the United States and is developing and conducting new pivotal studies to support device approval by the FDA. Ultimately, he aims to leverage this work to improve survival for patients with GBMs and establish FUS as a new therapeutic modality for GBM and other devastating brain diseases.

"It is a true honor to receive the Jolesz Award. To be selected for this award by the leadership of the Focused Ultrasound Foundation and Insightec is very meaningful given the important roles each of these organizations have played in establishing focused ultrasound in clinical practice. While I did not have the opportunity to meet Dr. Jolesz, his work and his life in neurosurgery and image-guided therapy are inspirations for me. Dr. Jolesz was a fearless pioneer and helped launch noninvasive, image-guided focused ultrasound therapy for numerous neurological disorders. I hope to embody Dr. Jolesz's spirit in advancing new devices and clinical applications of focused ultrasound."

In 2018, Dr. Woodworth was the recipient of the Foundation's Lockhart Memorial Prize and is a member of the foundation's GBM consortium, a multisite collaboration to streamline efforts and accelerate progress in using FUS to increase the body's antitumor immune response. He also serves on the foundation's Research Advisory Committee, a group tasked with ensuring that the External Research Awards Program supports catalytic research, creates awareness of FUS technology and techniques, and advances innovative clinical applications of FUS. Dr. Woodworth completed his undergraduate studies at Tufts University and earned his MD from the Johns Hopkins University School of Medicine.

At the symposium, Dr. Woodworth presented his lecture titled, "The Legacy of Dr. Ferenc Jolesz and the Emerging Era of Neurosonics." After crediting the large team of collaborators across many institutions and organizations for the success of Maryland's FUS brain program, Dr. Woodworth provided a brief background of the history of neurosurgery and its merging of MRI with ultrasound to create the field of FUS. He then shared an overview of his clinical trial work using FUS and microbubbles to disrupt the blood-brain barrier and treat patients with malignant brain tumors. He concluded by saying that FUS, which began with the vision of Dr. Jolesz, has now become a field that can deliver thermal, mechanical, and neuromodulatory forms of the energy with a high degree of precision, control, and monitoring.

.....

Andrew J. Lockhart Focused Ultrasound and Immuno-Oncology Postdoctoral Fellowship

The \$75,000 Andrew J. Lockhart Focused Ultrasound and Immuno-Oncology Postdoctoral Fellowship prize is awarded annually to recognize outstanding contributions in advancing cancer treatment using FUS and to support the recipient's potential for continued achievements in the field. The one-year fellowship is designed for early-career researchers as a way for the foundation to cultivate the next generation of investigators who could advance the development and clinical adoption of FUS in immuno-oncology. 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.



Yutong Guo, PhD
Georgia Institute of Technology
Stanford University

Yutong Guo, PhD, has been awarded the 2022 Andrew J. Lockhart Postdoctoral Fellowship in Focused Ultrasound and Immuno-Oncology. Dr. Guo completed her PhD at the Georgia Institute of Technology in 2021 under the mentorship of Costas Arvanitis, PhD, in the Ultrasound Biophysics and Bioengineering Laboratory. There, her research involved using low-intensity microbubble-enhanced FUS (MB-FUS) plus nanoparticles to improve the delivery of small interfering RNA in brain tumors. Her studies indicated that the therapy led to a 15-fold higher tumor cell death compared with nanoparticles delivered without MB-FUS. This work was also recognized with a Young Investigator Award. Dr. Guo will join Dr. Katherine Ferrara's laboratory at Stanford University in January 2023, where she plans to expand her research to study how low-intensity MB-FUS can be combined with chimeric antigen receptor (CAR) T-cell therapy to treat aggressive brain tumors, such as GBM.

"I am extremely honored and grateful to have been selected to receive the Lockhart Fellowship, which will support me to launch my independent academic career and conduct impactful research on the emerging field of ultrasound cancer immunotherapy," said Dr. Guo.

Andrew Lockhart's parents, Terry and Gene, said, "We believe it will take collaboration and revolutionary ideas to find effective immunotherapies for hard-to-treat cancers like the one that claimed our son Andrew. Our goal is to encourage a new generation of focused ultrasound researchers, and we are pleased to have Dr. Guo as the latest recipient of this fellowship."

"Dr. Guo has demonstrated a clear commitment to advancing the development of unique focused ultrasound and immunotherapy combination approaches," said Jessica Foley, PhD, the foundation's chief scientific officer. "This work could ultimately provide new treatments for hard-to-treat cancers, such as glioblastoma, where patients currently lack effective treatment options. We are excited to see what she accomplishes."

.....

Young Investigator Award Recipients

Young Investigator Awards encourage high-quality research and the presentation of meritorious scientific papers. Award recipients receive complimentary symposium event registration and up to \$2,500 for travel and lodging. On Thursday, October 27, the young investigators presented their research during lunch. The video of these presentations is available on the foundation's Symposium YouTube channel.

The 2022 Young Investigator awards, which were generously sponsored by Verasonics, are listed below.

Abdul-Kareem Ahmed, MD, for Bilateral MR-guided Focused Ultrasound Central Lateral Thalamotomy for Refractory Trigeminal Neuralgia: Preliminary Results

Javier Ajenjo Barcenas, PhD, for PAM and FUS-assisted AAV Delivery into the Brain for Quantitative PET/CT Imaging

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

Sheng Chen for Simultaneous Monitoring of Bone and Soft Tissue with a Rapid MRI Method for Focused Ultrasound Surgery

Riccardo Ciocca for A Noninvasive Biomarker of Microbubbles Distribution in the Brain: Comparison Between Intraoperative CEUS and Perfusion MRI

Daniel Dux, MD, for A 10-year Multicenter Experience of MR-guided High Intensity Focused Ultrasound (MRgFUS) in 105 Patients with Extra-Abdominal Desmoid Tumors

Areej Ennasr for Examination of Low-Intensity Focused Ultrasound (LIFU) Parameters and Longevity of Effect for Human Neuromodulation

Yutong Guo, PhD, for Microbubble Properties and Ultrasound Frequency can Modulate the Blood-Brain Barrier Phenotype

Alayna Hay, PhD, for Investigating the Ablative and Immunological Outcomes of Histotripsy Treatment for Canine Osteosarcoma

Alexander In for Low-Intensity Focused Ultrasound to Insula Attenuates Contact Heat Evoked Potentials and Reduces Pain Perception in Humans

Ayesha Jameel for The Evolution of Thalamic Ventral Intermediate Nucleus Targeting in MRgFUS Thalamotomy for Tremor, an International Perspective 2019 to 2021

Sara Johnson, PhD, for Non-Contrast MR Biomarker of Thermal Ablation in MRgFUS Treatments via Supervised Learning to MR-Registered Histology

Ryan Jones, PhD, for A Fully Electronically Steerable Modular MR-guided Focused Ultrasound Phased Array System

Stephen Lee for Focused Ultrasound Modulates Neuropathic Pain



View on the Foundation's
[YouTube channel](#) >



2022 Young Investigators

Xiaoyue Li for Real-Time Harmonic Motion Imaging Guided Focused Ultrasound (HMIgFUS) in Breast Cancer Patients in Vivo

Katherine Liu for Beta-Amyloid Changes in PET after Neuronavigation-Guided Focused Ultrasound Induced Blood-Brain Barrier Opening in Alzheimer's Disease Patients

Veronika Purrer, MD, for Quantitative and Qualitative Tremor Evaluation after tcMRgFUS Thalamotomy in ET

Lauren Ruger for Histotripsy Ablation of Spontaneously Occurring Canine Bone Tumors in Vivo

Tao Sun, PhD, for Focused Ultrasound Immunomodulation on the Myeloid Compartment of the Brain in Treating GBM and Alzheimer's Disease

Dezhuang (Summer) Ye, PhD, for Focused Ultrasound-Mediated Intranasal Delivery of AAV to Targeted Brain Regions with Minimal Systemic Exposure and Ultrasound with Microbubbles Accelerates Glymphatic Transportation

.....

2022 Young Investigators



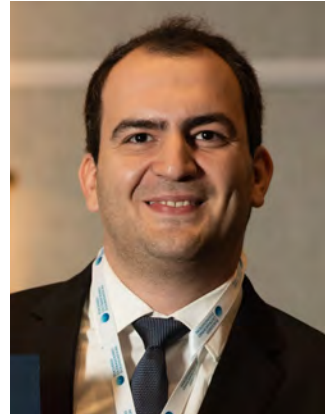
Abdul-Kareem Ahmed, MD

Bilateral MR-guided Focused Ultrasound Central Lateral Thalamotomy for Refractory Trigeminal Neuralgia: Preliminary Results



Javier Ajenjo Barcenas, PhD

PAM and FUS-assisted AAV Delivery into the Brain for Quantitative PET/CT Imaging



Ali Bassir, MD

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



Sheng Chen

Simultaneous Monitoring of Bone and Soft Tissue with a Rapid MRI Method for Focused Ultrasound Surgery



Riccardo Ciocca

A Noninvasive Biomarker of Microbubbles Distribution in the Brain: Comparison Between Intraoperative CEUS and Perfusion MRI



Daniel Dux, MD

A 10-year Multicenter Experience of MR-guided High Intensity Focused Ultrasound (MRgFUS) in 105 Patients with Extra-Abdominal Desmoid Tumors



Areej Ennasr

Examination of Low-Intensity Focused Ultrasound (LIFU) Parameters and Longevity of Effect for Human Neuromodulation



Yutong Guo, PhD

Microbubble Properties and Ultrasound Frequency can Modulate the Blood-Brain Barrier Phenotype

2022 Young Investigators continued



Alayna Hay, PhD

Investigating the Ablative and Immunological Outcomes of Histotripsy Treatment for Canine Osteosarcoma



Alexander In

Low-Intensity Focused Ultrasound to Insula Attenuates Contact Heat Evoked Potentials and Reduces Pain Perception in Humans



Ayesha Jameel

The Evolution of Thalamic Ventral Intermediate Nucleus Targeting in MRgFUS Thalamotomy for Tremor, an International Perspective 2019 to 2021



Sara Johnson, PhD

Non-Contrast MR Biomarker of Thermal Ablation in MRgFUS Treatments via Supervised Learning to MR-Registered Histology



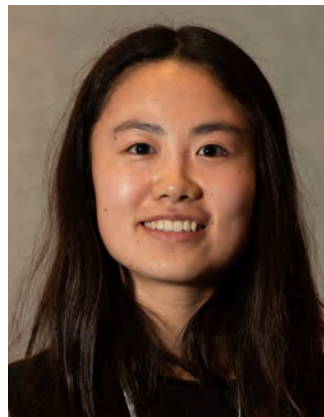
Ryan Jones, PhD

A Fully Electronically Steerable Modular MR-guided Focused Ultrasound Phased Array System



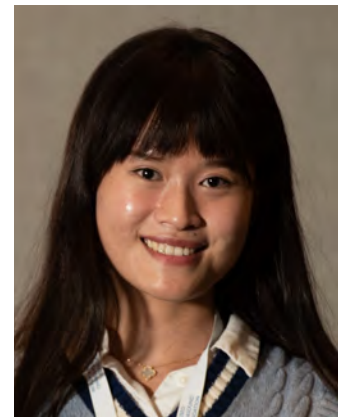
Stephen Lee

Focused Ultrasound Modulates Neuropathic Pain



Xiaoyue Li

Real-Time Harmonic Motion Imaging Guided Focused Ultrasound (HMIgFUS) in Breast Cancer Patients in Vivo



Katherine Liu

Beta-Amyloid Changes in PET after Neuronavigation-Guided Focused Ultrasound Induced Blood-Brain Barrier Opening in Alzheimer's Disease Patients

2022 Young Investigators continued



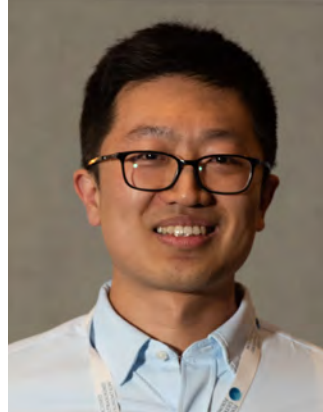
Veronika Purrer, MD

Quantitative and Qualitative
Tremor Evaluation after tcMRgFUS
Thalamotomy in ET



Lauren Ruger

Histotripsy Ablation of
Spontaneously Occurring Canine
Bone Tumors in Vivo



Tao Sun, PhD

Focused Ultrasound
Immunomodulation on
the Myeloid Compartment
of the Brain in Treating
GBM and Alzheimer's Disease



Dezhuang (Summer) Ye, PhD

Focused Ultrasound-Mediated
Intranasal Delivery of AAV to
Targeted Brain Regions with Minimal
Systemic Exposure and Ultrasound
with Microbubbles Accelerates
Glymphatic Transportation



Elizabeth (Swanee) Douglas,
University of Toronto

Global Intern Award

The Focused Ultrasound Foundation (FUSF) offers an international internship opportunity for high-school and university undergraduate students interested in the physical and life sciences. The global intern award is presented to the global intern receiving the highest peer-reviewed rating among submissions from the 2022 FUSF global interns. The award provides travel support to attend the symposium. **Elizabeth (Swanee) Douglas** from Sunnybrook Research Institute received the 2022 Global Intern Award for her abstract titled, “Investigation of Microbubble Response to Short Burst Phase Keying Ultrasound Exposures for Blood-Spinal Cord Barrier Opening.”

.....



Dezhuang (Summer) Ye, PhD

Bracco Women in Focused Ultrasound Award

The Women in Focused Ultrasound Award, sponsored by Bracco, was presented to the top scoring female young investigator. **Dezhuang (Summer) Ye**, PhD, received the award for her abstract titled “Focused Ultrasound-Mediated Intranasal Delivery of AAV to Targeted Brain Regions with Minimal Systemic Exposure” and “Ultrasound with Microbubbles Accelerates Glymphatic Transportation.”

.....

Monday, October 24, 2022



Honorary President's Address

Elisa Konofagou, PhD
Columbia University



Elisa Konofagou, PhD



View on the Foundation's
[YouTube channel](#) >

Dr. Konofagou thanked Dr. Kassell and the FUSF for the invitation. She presented “Ultrasound-mediated immunomodulation, neuromodulation drug delivery, and ablation.” For over 20 years, her team has investigated using ultrasound to immunomodulate, neuromodulate, deliver drugs, and for ablation. FUS, in simple terms, uses sound focused on a specific region while leaving the surrounding tissue intact. Throughout the 20th century, using sound properties to elicit biological effects was studied by various groups that led to increased understanding. In recent decades, with help from the FUSF and researchers around the world, there are now FDA approvals for FUS devices to treat uterine fibroids, bone metastasis, prostate cancer, essential tremor, and osteoid osteoma.

Dr. Konofagou’s earlier work examined using blood-brain barrier (BBB) disruption along with microbubbles for drug delivery. Using mouse models of Parkinson’s disease (PD), BBB disruption along with administration of neurotrophic factor could restore tissue in the striatum. Using the same model, her team demonstrated that gene delivery to the striatum could restore neural tissue. This research led to a clinical trial. She also described a mouse study for delivery of etoposide in a model of diffuse midline glioma (DMG) that increased brain concentrations 8 to 10 times with BBB disruption. A collaborative clinical trial of panobinostat and FUS in pediatric patients with GBM showed that BBB disruption can increase the concentration of the drug in the brain and provide tumor control.

FUS can also be used for immunomodulation. Microglia in the brain are mechanosensitive and activated by FUS BBB disruption. Additionally, greater pro-inflammatory mediators are released by BBB disruption, as well as anti-inflammatory mediators as a consequence of the BBB repair. FUS-induced BBB disruption enhances the phagocytosis of tau by microglia. Repeated FUS-induced BBB disruption reduces β amyloid and tau load, as well as improving working memory in mouse models of Alzheimer’s disease (AD).

Dr. Konofagou is transitioning some of the preclinical work to clinical trials for AD and pontine glioma. In a human clinical trial of BBB disruption in patients with AD, there were temporary reductions in β -amyloid in three out of six patients, suggesting a need for repeated treatment for a sustained effect. Another trial looking at BBB disruption for pediatric patients with pontine glioma has successfully opened the BBB in these patients; results are pending.

Dr. Konofagou described her work with neuromodulation. Early work in mouse models demonstrated that FUS could modulate motor and sensory responses. Ongoing work is looking at whether FUS can alter neuropathic pain sensations in post-surgical human patients. Patients who received FUS report decreased pain. Other projects include using 3D harmonic motion imaging for beam localization and monitoring of tumor ablation in real time.

.....

Monday,
October 24, 2022



Neal F. Kassell, MD

Founder and Chairman
Focused Ultrasound Foundation

Welcome

Neal F. Kassell, MD, founder and chairman of the Focused Ultrasound Foundation (FUSF), welcomed participants to the symposium. After 4 years, he was delighted to see so many people in person and virtually. Dr. Kassell set the stage by describing the three main objectives of the symposium: to create knowledge by sharing data and information, foster collaboration and innovation through personal relationships, and to have fun. This is the first hybrid meeting for the FUSF. In light of the changing format, the poster session was eliminated, and all scientific presentations were pre-recorded and continuously available. During the meeting itself, the aim was to encourage discussion and debate of hot topics through 27 panel discussions of experts. There was a robust mechanism in place through the app and meeting platform to interact with speakers and other attendees. As this was the first hybrid meeting, it was experimental and the first step in an iterative process.

Dr. Kassell wondered if participants felt that the international symposium was still valuable to them or if FUS had become well-incorporated into other scientific meetings so that this one is no longer necessary. Over the next 2 years, the foundation will offer an increasing number of in-person workshops and virtual roundtables. In closing, Dr. Kassell recognized the FUSF team that organizes the symposium, workshops, and meetings. The FUSF staff also works to fund research, produce webinars, podcasts, and blogs, as well as publish the newsletter and train interns.

.....



View on the Foundation's
[YouTube channel](#) >

Jolesz Award Winner Presentation

Graeme Woodworth, MD
University of Maryland School of Medicine



Graeme Woodworth, MD

Dr. Woodworth presented the Ferenc Jolesz Memorial Award titled “The legacy of Dr. Ferenc Jolesz and the emerging era of neurosonics.” Neurosurgery has improved from very basic surgical techniques in the 1900s to more sophisticated tractography that allowed interventions of deeper structures within the brain around 2011. Dr. Jolesz’s career focused on bringing together high-resolution imaging (magnetic resonance imaging [MRI]) with interventions. Dr. Jolesz founded the NIH National Center for Image Guided Therapy in 1995 and was the team leader of the first magnetic resonance-guided FUS (MRgFUS) therapy in 2005. This work proposed using thermal ablation to treat brain tumors with sub-millimeter accuracy. Beam steering was achieved by using subharmonic emissions for feedback in real time. Other work to come from this idea was using microbubbles injected into the bloodstream combined with low-power FUS for opening the BBB that has led to clinical trials using this method for patients with brain tumors.

Patients with glioblastoma (GBM) need more treatment options, as there are no treatments available outside of debulking surgery for the tumor. Clinical trials using controlled BBB disruption in patients with GBM undergoing chemotherapy were conducted and data analysis is ongoing to assess safety and feasibility. FUS BBB disruption increased neurovascular permeability during the study. The next steps are to treat residual invasive disease with a variety of chemotherapies. In summary, the field is able to deliver energy in different forms (thermal, mechanical, neuromodulatory) with a high degree of precision in a clinical setting controlled with closed-feedback loop monitoring

.....



View on the Foundation's
[YouTube channel](#) >

Movement Disorders: Tremor *Essential and PD*



Rees Cosgrove, MD, FRCSC

MODERATOR

Rees Cosgrove, Brigham and Women's Hospital

PANELISTS

Gordon Baltuch, Columbia University

Margaret Ferris, Stanford University

Pejman Ghanouni, Stanford University

Michael Kaplitt, Weill Cornell Medical College

Shayan Moosa, University of Virginia

Vibhor Krishna, University of North Carolina at Chapel Hill

Dr. Cosgrove presented on the current state of the art in magnetic resonance-guided FUS (MRgFUS) thalamotomy. For movement disorder, MRgFUS is used as an alternative to deep-brain stimulation (DBS) in certain patients: older adults (older than 70 years of age), medical high risk, averse to invasive surgery and permanently implanted DBS hardware, and willing to accept unilateral treatment. Around 160 MRgFUS thalamotomies have been performed at Brigham and Women's Hospital with an 80%–85% improvement in contralateral tremor, tremor near completely abolished in two-thirds of patients, and 80%–90% of patients experiencing sustained improvement at 2 years post-treatment. Common side effects tend to be mild and temporary, except paresthesia and imbalance. To achieve better results with future treatments, Dr. Cosgrove suggested improved accurate target selection and accurate lesion placement (size, shape, and extent).

Dr. Baltuch reported on FUS in low skull density ratio (SDR) cases ($<.4$). Patient selection is important because skull size and shape determine treatment success. In these patients, frame placement is key to maximize the number of elements in the transducer. Longer sonication times are usually needed. Dr. Baltuch concluded that patients with low SDR are treatable with careful planning.

Dr. Kaplitt raised two issues for discussion: 1) avoiding recurrence following MRgFUS thalamotomy and 2) the safety of bilateral MRgFUS lesions. He described a case of recurrence within 2 years after initial tremor control, highlighting the difficulty with lesioning. Tractography may help define the lesion, but additional tools are needed. Historically, treating the dominant hand was the only treatment. Patients have requested that both hands be treated, given the noninvasive nature of MRgFUS thalamotomy. The data on bilateral MRgFUS suggest that functional scores improve.

Dr. Ghanouni highlighted that the field needs to move beyond tremor reduction to optimizing quality of life (QoL). This is related to treatment planning to generate patient-specific ablation. The shape of the lesion spot will depend on skull geometry, which greatly influences the results.



View on the Foundation's
[YouTube channel](#) >

Dr. Moosa looked at patient-reported outcomes following MRgFUS for essential tremor (ET). Patients report an average 63% improvement in tremor control. Patient satisfaction remains high after 3–5 years. The ability to predict side effects as well as lesion size and shape will help improve patient satisfaction. Deep learning algorithms may eventually help with treatment planning.

Dr. Ferris discussed barriers to patient selection and recruitment for FUS in movement disorders. When polled, neurologists responded that they did not know what FUS is, felt that it was a step backward toward lesional work, preferred DBS, and noted reports of side effects in the 2016 Elias paper (40% of patients had stroke). When patients were polled on why they requested FUS, they noted: remotes for DBS were technologically challenging; infection with prior DBS; they do not qualify for DBS, do not want an implanted device, or do not have good support at home, or a family member had only partial improvement after DBS. Dr. Ferris summarized that general neurologists are unaware of FUS, and movement disorder neurologists are skeptical because of older data. The majority of studies are currently published in neurosurgical journals, and there needs to be a shift toward journals that neurologists are reading. Increasing involvement from residents would also increase awareness.

Dr. Krishna stated that the next phase is to optimize MRgFUS thalamotomy for each patient. Clinicians want outcomes that are reliable and struggle with the current landscape where outcomes are heterogeneous. There needs to be a target so that the procedure can be maximized to ablate the target in order improved target selection to avoid side effects from adjacent area ablation. This requires advances in tractography to encourage neurologists to recommend MRgFUS. It also requires advances in beam-shaping for a reliable and predictable heat map. There also needs to be a method to monitor accuracy; thermography measures increase in temperature but is not helpful with lesion shaping

1 Questions to all

How do you approach retreatment, and is there a role for gamma knife in this setting?

Dr. Moosa: In patients with reasonable SDRs, they would likely repeat MRgFUS and aim for a bigger lesion. Tractography has not been used much, but it will be used for future treatments. For patients with low SDR, DBS would be recommended.

Dr. Kaplitt: It is easier with MRgFUS to perform small lesions around the suspected target until the correct target is found, compared with invasive surgery. While recurrence is not a desired outcome, MRgFUS is a technology that lends itself to repeated treatments.

Dr. Baltuch: When patients have permanent side effects without tremor control, he would recommend DBS rather than MRgFUS. In the case of low SDR with failure, DBS or gamma knife would be an option. There are also cases where the stereotactic frame could have a better fit and additional treatment with MRgFUS could benefit the patient.

How do you know when you are done with the procedure?

Dr. Krishna: Focus on tremor reduction. He also suggested using an imaging-based approach. They identified VIM (ventral intermediate nucleus) as a region of interest (ROI) and ablate the maximum volume of that ROI during the procedure. Tractography can help with safety margins when targeting large volumes.

Are there patients that request MRgFUS thalamotomy that you turn away?

Dr. Cosgrove: Exclude patients who have terrible balance, use a walker, and live alone.

Dr. Ferris: Age itself was not an issue, but age combined with poor overall health would not make a good FUS candidate. As long as the patient has good balance, she would recommend FUS. Baseline dysarthria would also disqualify a patient for FUS.

Do you find it difficult to retreat intentional tremor?

Dr. Ferris: One side effect of treatment is dysmetria, which can look a lot like intentional tremor.

Dr. Krishna: We tend to treat all essential tremors the same and they are not. Essential tremor is a collection of different disease mechanisms that share a common phenotype. Patients with neuropathy and essential tremor often have worse outcomes; this is similar to the experience in DBS. Patients in their 80s with rapid onset tremor also tend to have worse outcomes. Sometimes with treatment, ataxia is unmasked, and these patients also have worse outcomes. More research is needed to identify the various syndromes within essential tremor.

.



Rees Cosgrove, MD, FRCSC

Movement Disorders: Parkinson's Disease *Dyskinesia/Motor/Dementia*

MODERATOR

Jose A. Obeso, HM CINAC (*Dr. Kaplitt became moderator*)

PANELISTS

Howard Eisenberg, University of Maryland

Brian Fiske, The Michael J. Fox Foundation for Parkinson's Research

Vibhor Krishna, University of North Carolina at Chapel Hill

Ying Meng, University of Toronto

Nora Vanegas, Baylor College of Medicine

Lloyd Zucker, Florida Neuroscience Institute

Dr. Obeso was unable to attend the meeting, so Dr. Kaplitt moderated the session and presented slides for Dr. Obeso. There are two types of FUS treatments for therapeutic applications in Parkinson's Disease (PD): high-frequency FUS for ablation and low-frequency FUS for BBB disruption. The most common surgical targets for functional treatment of PD include the thalamus, globus pallidus, and the subthalamic nucleus. These targets are difficult to treat because of the proximity to other sensitive structures. Tractography may help to increase targeting accuracy. Pilot studies of BBB disruption in patients with PD are ongoing. Preclinical research with BBB disruption and gene delivery have provided mixed results. Current and future challenges of high-frequency FUS include tremor recurrence after thalamotomy, risk of bilateral lesions, radiation safety versus efficacy, technical improvements (shaping the thermal spot to target and navigation), and earlier application.

Dr. Zucker explained that target selection is key to success. Research that classifies patients based on similarities in functional brain network activity can produce better outcomes by applying personalized brain analytics via machine learning. The team uses data from the Human Connectome Project to determine areas of brain activity that deviate from normal brain connectivity.

Dr. Eisenberg discussed ongoing clinical trials of bilateral FUS ablation for patients with PD. There is a trial for bilateral ablation of the pallidothalamic tract with 6 months between treatment of each side. The trial will mainly evaluate safety..

Dr. Krishna discussed optimizing treatment for PD. Diffusor tensor imaging (DTI) could be used to identify targets to deliver ablation in a standardized way. Currently, standard intraoperative monitoring is unreliable and may result in a mismatch between estimated target and tissue ablated, causing tremor recurrence or side effects. Tractography could be used to standardize target coverage.



View on the Foundation's
[YouTube channel](#) >

Dr. Fiske described the foundation's support for PD. They have funded early clinical trials on FUS for dyskinesia. More recently they have funded FUS-based brain "biopsy" and potential biomarker discovery. They also have created education materials on FUS for patients with PD.

Dr. Vanegas works on using FUS as a brain "biopsy." She also emphasized the importance of patient selection for FUS treatment. Selected patients are very heterogeneous and there is little data available on efficacy and the influence of disease features on outcomes and adverse events.

Dr. Meng works in the area of BBB disruption. She participated in a clinical trial looking at drug delivery of enzyme replacement therapy (acid- β -glucosidase enzyme (GCase) in patients with PD and glucosylceramidase beta (GBA) mutations (predisposition for PD). A pilot study in four patients was well tolerated. The next steps will be to treat additional patients and look at treatment efficacy.

1 Questions to all

What is the potential of combining ablation with BBB disruption and drug delivery?

Dr. Eisenberg: Approval of FUS studies is still a struggle, and FDA approval of ablation for PD is still ongoing, with additional refinement of the procedure necessary at this stage. BBB disruption for the delivery of therapeutics seems promising as well. Based on the current regulatory climate, he did not think that the FDA would allow combination treatment.

Dr. Kaplitt: Given that BBB disruption combined with a therapeutic can be repeated over many different sessions, this allows different therapies delivered to distinctive brain regions in separate BBB disruption sessions.

Dr. Krishna: DBS has limitations in that you can only stimulate one circuit. However, FUS can be used to target different circuits.

Is DTI reliable at the individual patient level?

Dr. Krishna: There are centers that perform DTI very well, and the idea is to replicate the successes. Each institution has its own systems and protocols, and results will vary between institutions. A lot more work on optimization of DTI is needed.

What is the difference in targeting between the different brain regions that are used with MRgFUS in patients with PD?

Dr. Eisenberg: Targeting the pallidothalamic tract has worked well unilaterally in pilot trials. He was undecided if this would produce better outcomes than targeting the globus pallidus internus (GPi). The use of tractography needed refinement.

Has cell replacement therapy been considered for PD?

Dr. Meng: We decided not to pursue cell replacement therapy due to the practicality of the therapy. The injection has to be delivered via an anterior line that also has to be compatible with the MRI suite.

Dr. Kaplitt: This is something under consideration. One challenge is that systemic treatments tend to circulate throughout the body and are not restricted to the brain.

2 Question to Dr. Zucker

Machine learning can be used with patient selection. Is there a system available that can do this?

There is currently no commercially available system that can do this in PD. There are a few partially vetted systems that are used in AD research. A common technology, such as machine learning, could help standardize treatment across centers, but more work is needed.

3 Question to all

There seems to be no consensus on GPi lesion size in PD. Do bigger lesions produce better outcomes

Dr. Krishna: GPi lesions seem to be limited by technical ability to ablate in the GPi, the individual patient's skull, and patient tolerability. More efficient heating in the globus pallidus would be helpful. The desired lesion size in the pallidum is larger than what is technically feasible at the moment.

Dr. Kaplitt: There is also concern with lesion targeting in the globus pallidus and targeting undesired tissue in the globus pallidus externus (GPe) or the optic tract. For PD, he also tracks thermometry in sensitive areas near the target.

• • • • •



Left to right

Ying Meng, MD

Howard M. Eisenberg, MD

Vibhor Krishna, MD

Neurodegenerative Diseases— Alzheimer's

MODERATORS

John Dwyer, Global Alzheimer's Platform Foundation

George Vradenburg, USAgainstAlzheimer's, Global CEO Initiative on AD

PANELISTS

Sandra Black, Sunnybrook Health Sciences Centre

Alexandre Carpentier, Hôpitaux Universitaires La Pitié Salpêtrière

Jin Woo Chang, Yonsei University College of Medicine

Jürgen Götz, University of Queensland

Ali Rezai, West Virginia University Rockefeller Neuroscience Institute



John R. Dwyer, Jr.

President

Global Alzheimer's
Platform Foundation



George Vradenburg

Chair and Co-Founder
USAgainstAlzheimer's
Global CEO Initiative on AD



View on the Foundation's
[YouTube channel](#) >

Mr. Vradenburg opened the session by pointing out that there has been a lot of change in the Alzheimer's Disease (AD) field in the past year. The approval of aducanumab in June 2021 was followed by a decision by Medicare not to cover monoclonal antibodies directed against amyloid. Another agent in development, lecanemab, has promising data with reductions in both tau and β -amyloid while slowing the rate of decline. The agents in development are all infusion products at this time. The lack of diversity in research slows the progress of precision medicines, and future work needs to include more diversity in order to better serve the patient population.

Mr. Dwyer described the goal of the Global Alzheimer's Platform Foundation: to reduce the time, cost, and efficacy of AD clinical trials for everyone. They are supporting and partnering on 15 clinical trials. FUS has great potential to increase efficacy and safety of agents for AD and may even help to lower costs.

Dr. Götz discussed specific brain areas for potential treatment with FUS. Frequency of treatment is an unanswered question. The long-term effects of FUS on AD pathology are unknown. Tau pathology starts in the entorhinal cortex and spreads to cortical areas while sparing the cerebellum, in contrast to β -amyloid that has a different pathology. There is no scientific consensus on what should be targeted for treatment.

Dr. Carpentier presented data from a pilot study of repeated BBB disruption (seven sessions) in patients with AD and an implanted Sonocloud device. Results from nine patients showed a small decrease (6.6%) in amyloid accumulation, and cognitive decline plateaued at 4 months. The next steps are to partner with other companies to look at whether combining BBB disruption with an anti-tau agent would produce a benefit for patients.

Dr. Chang presented data from a phase I MRgFUS BBB disruption in patients with AD. BBB disruption in the frontal lobe (36 cm³) was performed twice with 3 months between treatments. The data showed reductions in β -amyloid. Currently, a trial administering three BBB disruptions with 3-month intervals is ongoing to look at safety. The number of BBB disruptions that is optimal in human patients is unknown.

Dr. Rezai listed the advantages of FUS: no head shaving required, no stereotactic frame, and patients can go home the same day as the procedure. A safety and efficacy trial of FUS BBB disruption in patients with AD is ongoing at multiple sites. BBB disruption is used to safely open the hippocampus/entorhinal cortex, frontal, and parietal lobes with 2 treatments 2 weeks apart. Unpublished data suggest no deterioration in neurological or cognitive function versus a comparator group after 1 year as well as a focal reduction in β -amyloid. A clinical trial is underway looking at the combination of aducanumab with FUS BBB disruption.

Dr. Black reported on BBB disruption in patients with AD. FUS BBB disruption also may temporarily modulate bilateral frontoparietal network functional connectivity in patients with AD. Currently, multiple BBB disruptions in patients with AD are underway. Only a few patients have been treated so far. Future research could use this modulation in combination with monoclonal antibodies that are in development.

1 Questions to all

Will FUS allow targeting specific epitopes of tau or β -amyloid, or is the effect more general?

Dr. Götz: There is a debate in the AD community on whether tau is extracellular or intracellular. Tau is a much harder target, as a tau-targeted agent would need to cross the BBB and the extracellular membrane and engage with a neuron for effective clearance.

Dr. Black: There is a latent period of these proteinopathies, and β -amyloid is also a valid target. There are now blood tests or cerebral spinal fluid (CSF) screens to see if a person is at risk, and diagnosis is becoming more precise.

What are the regulatory opportunities and challenges for FUS with the FDA and CMS?

Dr. Rezai: The combination of FUS with a monoclonal antibody is a regulatory hurdle. Safety is a key regulatory concern and has significantly delayed the start of combination FUS trials. Timing of treatment is a future goal; patients should receive treatment prior to becoming cognitively impaired. Antibody doses are very high, which may lead to a greater risk of side effects. FUS could be used to lower doses.

Dr. Chang: Targeted treatment with monoclonal antibodies to specific brain regions may not be helpful. Depending on the extent of disease, multiple areas would need treatment. He felt that given what is known from preclinical research about repeated BBB disruptions, that information should be confirmed in human patients prior to treatment with a therapeutic agent.

Dr. Götz: The specific brain area that should be treated with FUS would depend on the AD pathology location.

2 Question to Dr. Carpentier

What is likely to be the best use of FUS in AD?

Some monoclonal antibodies can cross the BBB without FUS and demonstrate efficacy. FUS may help anti-tau antibodies enter the brain and penetrate the neuron.

3 Question to all

Is there another therapeutic area besides AD where the efficacy of FUS could succeed to draw additional interest?

Dr. Chang: Aducanumab is not the solution. The benefit of FUS for AD should be explored first, followed by combination with therapeutic agents.

Dr. Black: FUS is FDA-approved to treat essential tremor. The combination with antibody treatments is still in the early stages of determining the optimal brain areas for treatment.

.....

On monitor, left to right

Sandra Black, OC, O.Ont.,
MD, FRSC

Alexandre Carpentier, MD

Seated, left to right

George Vradenburg

Jin Woo Chang, MD, PhD

Ali Rezai, MD

John R. Dwyer, Jr.

Jürgen Götz, PhD



Keynote Speaker

Geoff Martha

CEO, Medtronic



Geoff Martha

CEO
Medtronic



View on the Foundation's
[YouTube channel](#) >

Mr. Martha discussed the origins of Medtronic, which was to create a battery-powered pacemaker. Their mission is to use technology to alleviate pain, restore health, and extend life. Innovation-driven medtech has three distinct phases: the invention of new markets, continuous innovation, and disrupting therapies in existing markets. FUS can be a disruptive technology. For example, while DBS is a common treatment for essential tremor, FUS has great potential because it is a one-time treatment without an implantable device. FUS also has the potential to treat liver cancer. FUS can treat liver tumors, particularly those that are close to sensitive structures like the aorta or diaphragm. To achieve impact at scale, the technology must work; clinical data are required; regulatory pathways need to ensure safety, quality, and efficacy; and appropriate payment models must be established. The development of Solitaire, a product that restores blood flow and retrieves clots in the brain for patients experiencing acute ischemic stroke, is an example. Strong clinical data helped with regulatory approval and reimbursement. Growing a market takes continuous innovation and drives adoption to expand into new markets.

The noninvasive nature of FUS can improve patient outcomes and quality of life. FUS treatment may benefit from machine learning or robotic guidance. Costs should be considered during the design phase so that FUS treatment is accepted by the health care market. Consider high-throughput facilities such as ambulatory care centers for FUS treatment. Another consideration is whether physicians treating this patient population have the required skillset, particularly in imaging, to perform FUS. Lastly, consider where FUS fits in the patient-centric ecosystem of care and where it could provide superior experiences and improved outcomes.

.....

Epilepsy

MODERATOR

John Rolston, Brigham and Women's Hospital

PANELISTS

Ellen Bubrick, Brigham and Women's Hospital, Harvard Medical School

Tiago Costa, Delft University of Technology

Nathan Fountain, University of Virginia

Vibhor Krishna, University of North Carolina at Chapel Hill

Max Wintermark, Stanford Bio-X

Hsiang-Yu Yu, Taipei Veterans General Hospital



John Rolston, MD, PhD



View on the Foundation's
[YouTube channel](#) >

Dr. Rolston stated that epilepsy develops in about 1.2% of the U.S. population and can severely impact a patient's life because of social stigma, difficulty completing school, finding work, and driving restrictions. Medications are first-line treatment for epilepsy, but about one-third of patients develop refractory epilepsy. Epilepsy surgery is very effective, and neuromodulatory treatment is an additional option. However, patients are hesitant to have surgery, and more options are needed.

Dr. Bubrick described the FUS procedure for epilepsy at her hospital. FUS is in the pilot safety trial phase in patients with temporal lobe epilepsy with six neuromodulatory sessions over 3 weeks targeting the hippocampus. It is easier to target and predict the energy pathway in this brain region because the temporal bone is thin and flat. Patients are monitored for up to 6 months. The study is ongoing and actively recruiting patients.

Dr. Krishna presented on targeting the anterior thalamic nucleus (AN) with FUS in patients with epilepsy. A phase 1 clinical trial for unilateral AN thalamotomy in patients with medication refractory epilepsy with high seizure frequency (>4 /month) is ongoing. The trial aims to enroll 10 patients; so far two patients have been treated. No serious adverse events have occurred, and both patients experienced a reduction in seizure frequency.

Prof. Costa discussed preclinical applications of FUS for epilepsy. In development are subcranial chips for EEG recording for seizure detection and high-precision FUS for activity inhibition. Some of the unique challenges for these subcranial chips are the energy source (battery size, longevity), target localization (closed-loop operation), and biocompatibility. An implantable chip could decrease costs associated with FUS hardware.

Dr. Yu reported on a series of experiments and studies of FUS for the treatment of epilepsy. A preclinical study showed that transcranial FUS suppressed epilepsy. A pilot study of drug-resistant epilepsy in six patients demonstrated safety. A pilot study (single-blind, randomized, crossover study) to evaluate the safety and efficacy of the NaviFUS System neuromodulating treatment for patients with drug-resistant epilepsy is ongoing. Additional studies are waiting for institutional review board (IRB) approval and include

an investigation of brain connectivity modulated by FUS using intracranial cortico-cortical evoked potential (CCEP) and an investigation of high-intensity focused ultrasound (HIFU) for epileptogenic focus lesioning with the Exablate Neuro system (Insightec).

Dr. Fountain described lesioning work with HIFU in a pilot study of up to 20 patients. With the development of autofocusing, it is easier to enroll patients. These patients were selected for surgery, which was carried out with HIFU, and had hypothalamic hamartomas. Patients had a single-session HIFU treatment and were followed for up to 12 months. The procedure requires head shaving and a stereotactic frame; the study is ongoing.

1 Questions to all

1 The ongoing studies described seem to have low enrollment. What might be causing this?

Dr. Krishna: Some of the patients do not want to shave their heads. Transportation issues along with a reliable caregiver to take the patients to all of the appointments can be a challenge, as the patients themselves cannot drive. The field also needs to identify how to integrate these kinds of trials into the treatment paradigm.

What are the potential advantages of HIFU over laser interstitial thermal therapy (LiTT)? Secondly, can general anesthesia be used to obtain larger ablation volumes?

Dr. Wintermark: A lot of patients interested in FUS are looking for something that seems easier than LiTT. However, FUS is more cumbersome than LiTT, although FUS is noninvasive while LiTT is minimally invasive. Improvements in FUS technology should help attract patients. He also agreed that general anesthesia would allow a larger treatment volume, but the patient needs to be awake to monitor for skull overheating. Patients that seek out FUS usually do so because they are looking for alternatives to standard treatments, and when they learn more about a clinical trial, are not always interested because of the amount of involvement required.

Dr. Bubrick: LiTT might be considered minimally invasive, but it is still quite invasive and carries the risk of hemorrhage. FUS is more appealing than open craniotomy for most patients.

• • • • •

Psychiatric Disorders

MODERATOR

Benjamin Greenberg, VA RR&D Center for Neurorestoration and Neurotechnology

PANELISTS

Raag Airan, Stanford University

Jean-François Aubry, Physics for Medicine Paris

Renana Eitan, Brigham and Women's Hospital

Noah Philip, Brown University

Ali Rezai, West Virginia University Rockefeller Neuroscience Institute



Benjamin Greenberg, PhD, MD



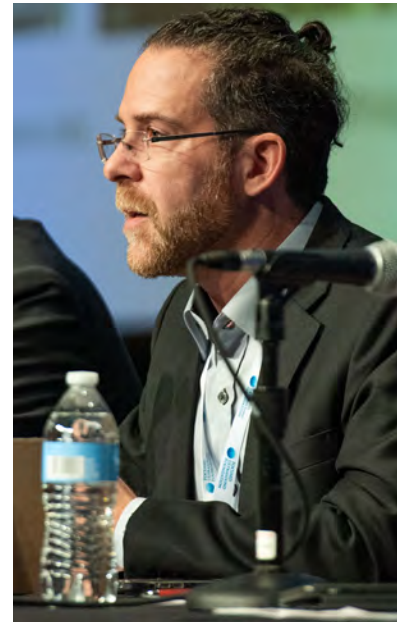
View on the Foundation's
[YouTube channel](#) >

Dr. Greenberg stated that psychiatric disorders, including substance misuse, accounts for 25% of all disability worldwide. Both low-intensity FUS (LIFU) and high-intensity FUS (HIFU) have potential as treatments for psychiatric disorders. FUS is useful for neuromodulation because it is noninvasive and reversible, has the ability to target brain regions with millimeter resolution, has no important off-target activity, has robust anatomic variation, and has predictable effects. Safety questions remain, including edema, microhemorrhage or any clinical injury, neurological changes on exam, neuropsychological changes on testing, sustained worsening of psychiatric symptoms, headache and sedation, and acoustic artifact.

Dr. Aubry presented on inducing a strong target engagement with high-precision transcranial targeting. Low-cost systems can compensate for the aberration correction, despite the skull bone, to reach the intended target. There are two methods to accomplish this, either with multiarrays or a single-element transducer with a lens for correction. The biggest question in the field is what are the best targets for neuromodulation in psychiatric disorders.

Dr. Philip discussed the potential for reversible DBS in psychiatric illness. Psychiatric illness is associated with a great deal of disability, and current treatments are inadequate. An ongoing study of LIFU to treat depression and anxiety is looking at safety and tolerability of disrupting amygdala activity. One of the core challenges is to develop a biological readout for the beam path.

Dr. Rezai emphasized that psychiatric disorders are very common. FUS has the potential to treat large numbers of people because it is noninvasive and frameless, has no temperature increases with LIFU, and has same-day outpatient treatment potential. A pilot trial of LIFU neuromodulation of the nucleus accumbens for substance use disorder is underway with the primary objective of safety, tolerability, and feasibility. Two patients have been treated, and their response indicates that there may also be some effect on daily craving ratings. The next step will be a larger study to investigate dose and timing, both subacute and long-term, as well as assessing other factors associated with relapse (e.g., cognitive functioning) and functional brain imaging.



Top left

Seated, left to right: **Benjamin Greenberg**, PhD, MD; **Ali Rezai**, MD; **Noah Philip**, MD; and **Jean-François Aubry**, PhD,

On monitor, left to right: **Raag Airan**, MD, PhD, and **Renana Eitan**, MD

Top right

Noah Philip, MD

Dr. Eitan spoke about the implementation of advanced surgical neuromodulation treatments in psychiatry. DBS has had little impact on the lives of psychiatry patients, partially because of a lack of first-class clinical research in this field. More standardized clinical trials need to be carried out. MRgFUS bilateral capsulotomy for the treatment of obsessive-compulsive disorder (OCD) is a planned pilot study to look at safety, followed by a randomized, sham-controlled, double-blinded stage. Patient enrollment will begin soon.

Dr. Airan described a planned clinical trial under consideration with the FDA. The proposal is for FUS-targeted drug delivery of nanoencapsulated drugs that are FUS-sensitive and that will release the drug of interest upon irradiation. They hope to begin a trial in about 18 months with targeted ketamine delivery to the anterior cingulate for patients with chronic pain that will focus on safety. One of the biggest unanswered questions in the field is the biological outcome measures that are most relevant in a psychiatric context.

1 Question to Dr. Aubry

How do we know that we are getting the biologically active intensity or pressure at the target?

Dr. Aubry: Simulations can be used to estimate the effect of the skull bone on the transmission coefficient. Further work is needed to validate these models. The amount of energy needed at the target is still undecided in the field. At this point, a functional response should also be defined.

Dr. Philip: LIFU systems that can operate with EEG or MRI that allow real-time readouts are needed.



Left to right

Jean-François Aubry, PhD

Ali Rezai, MD

2 Questions to all

What might treatment look like in the future for patients with OCD?

And what type of patients might benefit from this kind of treatment based on severity and clinical features?

Dr. Eitan: In the future, the idea is to treat less severe patients with LIFU. The beneficial brain region for modulation is undefined at this time and will likely vary for each patient. Patients with chronic OCD will probably need irreversible lesioning. Less-invasive treatment can be used to localize the optimal brain location for each patient.

Dr. Rezai: DBS is challenging because of the constant need for monitoring of an implanted device. FUS has the potential for acute or subacute management of psychiatric patients. His team was surprised by the persistent reductions in anxiety and cravings in patients treated with FUS. The noninvasive nature of FUS combined with the ability to modulate certain brain networks could make it very useful in combination with medications and therapy. In the long-term, the outlook for FUS should surpass DBS.

How repeatable across centers is DTI?

Dr. Philip: Repeatability of FUS treatment depends on the patient, but there are common themes. Personalized treatment is key to success and there may be no single treatment location that works for all patients.

.....

Why Advocacy?

MODERATOR

Jessica Foley, Focused Ultrasound Foundation

PANELISTS

Katie Collins, G2G Consulting

Hugo Embert, EDAP TMS

Patrick Hope, Medical Imaging & Technology Alliance (MITA)

Noah S. Philip, Brown University



Jessica Foley, PhD

Dr. Foley introduced the issues: For years, the FUSF has amplified its governmental advocacy efforts for two reasons. Some FUS applications have been approved treatment options for many patients, but access to these treatments is lagging. Furthermore, there are innovative and emerging uses of the technology that have the potential to improve the lives of many patients and would benefit greatly from increased research funding.

The goal here is to address challenges limiting successful commercialization and access to FUS therapies. The key message is: research, access, education. Three barriers are prominent:

- Lack of awareness of FUS and its potential,
- Lack of insurance coverage and reimbursement, and
- Lack of research funding to advance new FUS treatments, particularly for conditions prevalent among veterans and service members.

Advocacy partners include G2G Consulting, the Medical Imaging and Technology Alliance, other trade associations, FUS industry, physicians, and patients. Ongoing activities have focused primarily on the United States.

Ms. Collins noted that G2G has worked with FUS for several years. They have a background in health policy and recognize the importance of research funding.

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) are important potential partners of FUSF because many uses of FUS align with their population of patients. It is important to be sure they are aware of the possibilities of FUS, and then to be sure that coverage is provided. As to funding, DoD is a huge contributor of grants for this sort of research, as are the Defense Advanced Research Projects Agency (DARPA) and Congressionally Directed Medical Research Programs (CDMRP).

Moreover, the government currently is ripe for positive change. Government officials are beginning to understand transformative technologies, and now, advocacy will make a difference because those officials are receptive.

Mr. Embert thought that making the general public aware of FUS and its potential will require much work. By default, CMS lists new technologies as “no reimbursement,” and many moving parts are engaged in trying to get reimbursements. Often, it is a question of



View on the Foundation's
[YouTube channel](#) >



Left to right

Jessica Foley, PhD;
Noah Philip, PhD;
Patrick Hope, MA, JD;
and **Katie Collins**

understanding the technology, which is just a matter of collaborating. We need to provide context and help on how policies are made, and how policymaking can be influenced. Patients are important because they can explain how life-changing a technology FUS is. Patients' explanations remind the researcher why she or he is doing the research in the first place.

Mr. Hope said MITA has partnered with FUS since 2018. MITA represents 90% of the entire medical imaging market and it supports efforts for reimbursement and insurance coverage, i.e., MITA involvement implies that the entire industry is behind this push. If we do nothing, it would take decades to achieve wide spread access for FUS. We need to advocate to move toward FDA recognition and CMS coverage and reimbursement.

MITA meets with policymakers on Capitol Hill and advocates from the patient perspective and from industry's perspective. Other efforts include letters to the editor of various publications, or other types of meetings. MITA also works with artificial intelligence (AI) companies, positron emission tomography (PET) companies, and others that could benefit. It is important that FUS have the support of the entire industry - "advocacy is a contact sport."

Dr. Philip recognized FUS's tremendous potential but said it is largely unknown in the nonspecialist world. At the same time, investigators must get research funding, e.g., from CDMRP. To interest key stakeholders, involving patients is important. Their stories move

people's minds and get them engaged. Similarly, investigators should ask for patients' input at the inception of the project (not just when writing the proposal) and continue getting that input throughout the project. In conclusion:

Now is the right time to use advocacy.

Join the FUSF in their advocacy efforts.

Send your local congressman a press release, and, as important, use social media.

Most of all, involve your patients; they can be partners in advocacy.

Meanwhile, scientists need to do their best research.

Discussion

Mr. Hope: CMS is developing a new pathway that will streamline the process of getting from FDA approval to CMS reimbursement. When that policy comes out, FUS community support will be needed.

Mr. Embert: Companies and researchers may not appreciate the time involved to provide input to these policies, but without that input, FDA clearance cannot get to the finish line for payback of investors and reimbursement of patients. Collaborating with other companies is extremely important. People who have gone through this process know, for example, how the FDA and CMS systems work.

Dr. Foley: Access to new technologies must be equitable. We need to develop champions to help achieve our goals of widespread patient access to FUS.

Ms. Collins: Participants are encouraged to contact FUSF or G2G to sign up to get involved in our advocacy efforts. Everyone must be involved; it matters whether many people write to their representatives. G2G wants to know what the challenges are for investigators and how G2G can help.

.

Trials and Tribulations of Startups

MODERATORS

Randy Castleman, Focused Ultrasound Foundation

Patrick Edelmann, Focused Ultrasound Foundation

PANELISTS

Bradley Horowitz, Google

Michael Marquez, Morado Ventures

1 Questions to both

How do you differentiate between a viable opportunity and a bright idea that will go nowhere?

Mr. Horowitz: Ideas are important, but much rarer are entrepreneurs who can execute those ideas. The initial idea may be a progressive act to adapt to the inside and outside world; therefore, you need someone who can pivot and dynamically change with the challenges. Most of these ideas are long odds, but a certain prototypical individual can do it.

Mr. Marquez: There are thousands of ideas, but they must be assessed for whether this is a venture idea with a 10X or 100X return, or just a good business idea.

People must understand the market opportunity to provide context. Then it rests on that person to build the team that will do the work.

Personal money vs. venture capital is evolving. Before, the field was composed of a cottage industry of angel funds (Google's startup funds); now there are three stages of development, and at each stage, a different kind of funding is needed. The creator must look at the pre-seed and seed stage to evaluate the project by asking how a consumer or service could use this product. Evaluation is based on what this could become. Then you move into a seed and series process, evaluating whether the company has revenue and expenses. The funder's role is to enable the entrepreneur to access the needed funds easily.

Mr. Horowitz: In those early stages, people are looking for ways to bootstrap their idea into the next level of viability, e.g., hiring staff, so you need a company discussion during the first 6 months. Then the project progresses from seed to late-stage to initial public offering (IPO).

Mr. Marquez: It is incredibly macro-dependent. Recently, it has become more difficult to get starter funds (angel funding is the least structured). The next round of financing is the pre-seed and seed together. In the first two rounds the funder gives about 20%; then less and less. About half the companies are eliminated after the initial stage; 30% more by the next stage, and 1% near the finish. There's less and less dilution as you proceed along the lifespan of the company.

Information transfer has greatly speeded up in many industries, and now in the venture industry. Here it happened much faster than previously, and companies react to that.



View on the Foundation's
[YouTube channel](#) >



Left to right

Randy Castleman
Patrick Edelmann

Cycles are not gone. We will see the speed of information flow and much shorter information lag.

Mr. Horowitz: The outcomes of an initial investment are a decade away, and the world will look very different by then, so flexibility is paramount. Later-stage companies have to figure out how to deal with the whatever the current crisis is. They must be sensitive to the “cash-burn”, and they must structure the company to weather these downturns. Many companies came back fairly quickly from the COVID crisis, so there’s a fair amount of money in the system. This is part of the bias issue with a lot of investors in half-finished projects. Also, it is not possible to remove the emotion aspect of what is going on in the world, the daily doom and gloom. So, there’s a bit of a wait-and-see period.

In the incubation period, can you identify red flags?

Mr. Horowitz: One red flag is over-optimization. People become infatuated with hard technical problems and forget that the goal here is to build a business. They tend to over-optimize and over-invest early on when they build a system. Another red flag is absence of the ability to keep in mind the market impact of the technological development when people are solving problems.

Mr. Marquez: When funding a product, the most difficult question is how to know when it is working.

What about the idea of trying to time fundraising with value inflection points?

How do you know what is a value inflection point?

Mr. Marquez: You have to break down a financing trajectory, so it makes sense in your own business plans. This is incredibly hard to do; so many companies try to build themselves to be bought out, which is incredibly risky.

What advice can you offer?

Mr. Marquez: Do not get greedy. You can raise some funds now and more later when they are needed. If you get the timing wrong, you are out of business. So, you need to figure out at each stage the amount of money you need to complete that stage and move on to the next one, so you're not having to fundraise while working on the project.

Mr. Horowitz: Companies fail because they run out of money. The only thing you need to do with your seed money is to get to level A; then raise funds for the next round. You will have irrefutable evidence that you can raise those funds. You have to create narratives that have a compelling story. Many obstacles are outside one's control, making the ones inside your control more important.

What positive note do you see right now?

Mr. Marquez: Innovation and technology are being created, and simultaneously the pace of technological adoption is speeding up. Now we have generations who have grown up in a digital space. It feels like we are in inning 1 of this incredible revolution. In addition, the entry price for investors is encouraging for 2 or 3 years down the road.

Mr. Horowitz: Great companies are started in periods of downturn when people getting laid off are on the sidelines looking for something else to do. At the same time, people of questionable ability are "washed away." Technology, e.g., AI, or large language models, are really accelerating, similar to mobile computing and social computing. It is exciting to watch this level of innovation as it happens.

.

Tuesday, October 25, 2022



Tuesday,
October 25, 2022



Jason Sheehan, MD, PhD
Professor of Neurosurgery
University of Virginia



Graeme Woodworth, MD
Professor and chair of neurosurgery
University of Maryland
School of Medicine



View on the Foundation's
[YouTube channel](#) >

Brain Tumors— Glioblastoma

MODERATORS

Jason Sheehan, University of Virginia

Graeme Woodworth, University of Maryland

PANELISTS

Ko-Ting Chen, Chang Gung Memorial Hospital

Nir Lipsman, University of Toronto

Serena Pellegatta, IRCCS Istituto Neurologico Carlo Besta

Francesco Prada, Istituto Neurologico C. Besta

Adam Sonabend, Northwestern University

Dr. Sheehan provided an overview of GBM, the most common primary malignant brain tumor in adults. Treatment is based on size, location, type, and grade of tumor as well as the patient's goals and overall health. The benefits of FUS treatment are that it is noninvasive and targeted, has no systemic risk and minimal local risk, and can be repeated safely. There are a variety of FUS systems in development for GBM treatment. BBB disruption is the most commonly explored treatment option. Therapeutics tested so far include temozolomide, bevacizumab, carboplatin, and paclitaxel, all of which cross the BBB at some level without BBB disruption. Sonodynamic therapy uses a nontoxic substance known as a sonosensitizer (5-aminolevulinic acid (5-ALA)), which accumulates in tumor cells and can be converted into an activated substance with tumoricidal effects when activated by ultrasound beams. FUS with microbubbles or mild hyperthermia combined with radiation is also being explored as a radiosensitizer. This research may increase efficacy and decrease tumor resistance to radiation.

Dr. Sonabend described a dose-escalation trial with albumin-bound paclitaxel and the Sonocloud implantable system. There was a reversible dose-limiting toxicity, and the trial helped finalize the dose for a phase 2 study. Another trial recently opened to investigate the effects of the technology in the peritumoral brain and found an increase of 4–6 times the baseline levels of the drugs (carboplatin and paclitaxel).

Dr. Lipsman described trials with the Exablate system. An early trial of BBB disruption in combination with doxorubicin had good safety data, and this was expanded to a larger multicenter trial, where FUS-mediated BBB disruption is used in combination with maintenance chemotherapy, and this trial recently completed. Another trial is applying FUS-mediated BBB disruption along with carboplatin in patients with recurrent GBM. Over time, a larger tumor volume and procedure efficiency have been implemented. The current GBM work is measuring cell-free DNA (cfDNA) pre-operatively in patients undergoing surgery for GBM.



Left to right

Graeme Woodworth, MD

Francesca Prada, MD

Ko-Ting Chen, MD, PhD

Dr. Chen reported on a phase 1 clinical trial in patients with recurrent GBM that was recently completed. A trial is ongoing with the NaviFUS system and bevacizumab to enhance drug treatment delivery at the tumor margin. The treatment protocol was biweekly treatment with two sonications per treatment session. There were six patients enrolled and 83% were progression-free at 6 months. A larger phase 3 trial is needed to confirm results.

Dr. Prada explained that they are using the Insightec system in clinical trials. The first was a small trial of three patients of BBB disruption with temozolomide maintenance treatment. This was followed by treatment with cisplatin in patients with recurrent GBM. A sonodynamic therapy trial using 5-ALA in patients with newly diagnosed GBM is planned.

1 Question to Dr. Sonabend

How does a 4-fold increase in paclitaxel translate to the amount of drug in the tumor over time?

This is a great question, but drug levels were only measured 45 minutes after sonication, so this is unknown. It will be important to understand the duration of these agents in the brain after the BBB closes.

2 Questions to all

When you are targeting the tumor margin, what method is used to find the margin?

Dr. Lipsman: Fluid attenuated inversion recovery (FLAIR) is useful for targeting remaining tumor cells and other pathological processes. Since this can be a large volume, the team also tries to sonicate as large a volume as possible.

BBB disruption is trying to achieve a certain bioeffect, but usually the result is heterogeneous. Are there other ways to measure bioeffects or standardize treatment?

Dr. Lipsman: This is a field with more questions than answers. It depends on how outcomes are defined. There is large variability in cavitation doses, and this depends somewhat on the tissue that is being sonicated. Safety is important during the procedure, as well as the ability to measure cavitation dose in real time. There are a variety of tissue attributes that affect the energy dose and the duration that the BBB will be open, such as previously irradiated, highly vascularized tissue, gray versus white matter, necrosis, and swelling. The factors that are most important for safety are still undecided and under investigation. At the moment, contrast-enhanced imaging is most useful for monitoring during the procedure.

Dr. Prada: MRI is used at the end of the procedure to confirm BBB opening. Another factor to consider is the microbubble distribution measured during the procedure by cavitation detection. Early work suggests that bubble distribution could be used as a biomarker and to guide acoustic dose.

Dr. Sonabend: With the Sonocloud device, the FUS energy does not have to cross the skull and the energy distribution is fixed. Fluorescein is sometimes used to confirm BBB opening, but they do not check every treatment. The Sonocloud device is already programmed to work with microbubble injections and the timing is set by the device software.

Dr. Chen: The NaviFUS device is not integrated with MRI, and confirmation of the BBB opening is not done for every treatment. Acoustic monitoring is used to check the BBB opening and safety during treatment.

Has anyone looked at the duration of BBB opening or timing of drug delivery to optimize the effects of a given therapeutic?

Dr. Lipsman: This seems to vary across patients. Imaging at 24 hours following the procedure shows that the BBB is closed. The variables seem to be tumor tissue, area of sonication, and the degree of edema. These all factor into how long the BBB is open.

Dr. Sonabend: Their experience has been that the BBB closes within 1 hour after treatment and peak plasma levels usually occur at the end of drug infusion.

What is the best way to monitor the injection of bubbles to maximize treatment?

Dr. Sheehan: The best way to monitor microbubbles is still unresolved. The infusion is usually given at a continuous rate during the procedure. The degree of perfusion in GBM tumors varies widely.

Dr. Chen: We assume that the microbubbles phase out within 5 minutes and perform two sonications within 5 minutes.

Dr. Sonabend: A bolus injection is given immediately prior to sonication; the machine software provides instructions on timing of the microbubble injections. He cautioned that with larger doses of microbubbles there is a greater risk of intracranial bleeding.

What does the future look like and what could rapidly advance the field?

Dr. Lipsman: There is an urgent need to develop additional therapeutics for GBM. Further institutional collaboration on the technical side to define specific ultrasound parameters are needed to maximize therapeutic delivery. Regulatory hurdles are some of the greatest challenges at this time and are usually the most time-consuming piece of these clinical trials. Standardized outcome measures are also needed.

Dr. Prada: Refining the treatment to be less cumbersome and available to patients could increase the frequency of treatment, which might be necessary to see effectiveness in this setting.

Dr. Chen: FUS could become an additional treatment option for GBM and optimize treatment for these patients.

Dr. Sonabend: This technology is still in the early stages of development, and we should not assume that the preclinical biology is the same in humans. There are still basic questions that are not well understood in human patients. For example, how long does the drug stay in the brain, what happens when an enhancing lesion is sonicated, and is there any benefit? Before more efficacy trials are conducted, we should understand the biology a little better.

.....

Seated, left to right

Graeme Woodworth, MD

Francesca Prada, MD

Ko-Ting Chen, MD, PhD

On monitor,

clockwise from top left

Adam Sonabend, MD

Nir Lipsman, MD, PhD, FRCSC

Jason Sheehan, MD, PhD



DIPG

MODERATOR

Stergios Zacharoulis, Columbia University

PANELISTS

Kevin Beccaria, Assistance Publique-Hôpitaux de Paris

Javad Nazarian, Children's National Hospital

Roger Packer, Children's National Hospital

James Rutka, Toronto SickKids

Luca Szalontay, Columbia University Irving Medical Center

Dannis van Vuurden, Princess Máxima Center



Stergios Zacharoulis, MD, PhD

Associate Director
of Pediatric Oncology
Columbia University



View on the Foundation's
[YouTube channel](#) >

Dr. Zacharoulis introduced the topic of diffuse midline glioma (DMG) treatment with FUS. DMGs harbor the H3 K27M mutation, including diffuse intrinsic pontine glioma (DIPG) and are lethal high-grade pediatric brain tumors. Current standard of care is radiotherapy. FUS is being investigated for treatment of DIPG using several devices, including Insightec, TheraWave, NaviFUS, and Carthera. Preclinical data suggest that FUS-mediated BBB disruption is safe and reversible, but no survival benefits have been found. Further work in preclinical models will evaluate additional models to assess survival benefit, address tumor heterogeneity, and carry out pharmacokinetic and pharmacodynamic modeling. There are several early-phase clinical trials with FUS in pediatric patients.

Dr. Packer stated that there has been no progress in DIPG in over 3 decades. Most patients have non-enhancing tumors. Preclinical research that demonstrates efficacy often does not translate to the human patients with DIPG. The first human study involving focused ultrasound was with 5-ALA, and the trial is currently recruiting. Two children have been treated; treatment occurs after radiation and before recurrence. They are also participating in a multicenter trial of FUS-mediated BBB disruption combined with doxorubicin and are enrolling patients. Doxorubicin may not be the best chemotherapeutic, but it has established safety and efficacy.

Dr. Szalontay reported that preclinical research showed that FUS BBB disruption in the brainstem was safe. Panobinostat was also shown to extend survival in a preclinical model. This led to a clinical safety study of FUS combined with panobinostat treatment of three patients with DIPG. Toxicity included skin irritation at the site of FUS. Two out of three patients reported symptom reduction. Panobinostat was removed from the U.S. market and etoposide is now being studied instead. Further research into drug combinations, particularly checkpoint inhibitors, are also being considered.

Roger Packer, MD

*Senior Vice President, Center for
Neuroscience and Behavioral Medicine
Director, Gilbert Neurofibromatosis
Institute Director, Brain Tumor Institute
Children's National Hospital*



Dr. Beccaria provided an overview of a phase 1 trial using the Sonocloud 9 device for the first time in pediatric patients to look at safety and feasibility. Carboplatin will be used as a therapeutic. The trial will also look at dose escalation of acoustic pressure. It is currently recruiting patients.

Dr. van Vuurden described a clinical trial planned for 2023 that will enroll patients with DIPG (10 adults and 10 children) and will administer FUS-BBBO combined with temozolomide to look at safety and feasibility. There is another study in the planning stages for patients with AD. They are looking at pharmacokinetics in preclinical models. Further trials are planned with FUS and combination treatments of immunotherapy (CAR-T cells). Collaboration with other groups will strengthen these studies so that best practices can be shared.

Dr. Nazarian discussed sonodynamic therapy with FUS. They are also analyzing patient plasma samples for potential biomarkers and have been able to measure circulating tumor DNA (ctDNA) from CSF and plasma. Collected ctDNA can potentially provide information on the degree of BBB opening as well as information about the tumor. There is a lack of animal models for FUS; larger animals are needed to look at BBB disruption with FUS in the treatment of DIPG.



Left to right

Luca Szalontay, MD

Stergios Zacharoulis, MD, PhD

Roger Packer, MD

1 Questions to all

What is the best method to measure BBB opening?

Dr. Zacharoulis: We used contrast-enhancement, but sometimes were unable to confirm BBB opening.

Dr. Packer: We do not use any imaging for sonodynamic therapy. We are using ctDNA in some of the planned trials to gain information on BBB opening. For the BBB studies in children, there are limits on sedation time and amount given to patients who have previously received radiation. Currently, there is a presonation MRI scan, a post-FUS MRI scan, and one additional MRI scan 24-hours postsonication.

Dr. van Vuurden: Radiolabeled monoclonal antibodies are being used, when possible, but may not be possible at every center due to the need for a cyclotron.

Dr. Beccaria: They also use pre- and post-sonication MRI scans with contrast enhancement.

Biomarker evaluation in DIPG is difficult. Can you explain how you will address this?

Dr. Szalontay: For the etoposide study, we will collect serum (pre- and post-sonication, and 4–6 hours after sonication) to analyze cfDNA. They will use the MSK-IMPACT test that analyzes 500 cancer-related genes. They want to look at tumor response to treatment as well as attempting to predict progression. They will also measure the effects of etoposide on the tumor.

Can you discuss trial coordination?

Dr. Nazarian: The multicenter trial model will allow sharing of tissue samples to allow the site with the greatest expertise to analyze the data instead of one site trying to perform all the assays and analysis involved.

Can you address how to monitor safety in these studies?

Dr. Szalontay: There are differences in the length of time that elapses for the BBB to close. Closure time will be determined for each patient, and that will be used to determine the frequency of FUS treatment.

Dr. Packer: Patient selection is very important for these early-phase trials. Patients with stable disease should be selected for studies.

2 Question to Dr. Beccaria

What other treatments will be investigated in addition to carboplatin?

We will also be looking at some radiosensitizers that could be used in combination with FUS.

3 Question to Dr. van Vuurden

Can you address how to monitor safety in these studies?

Dr. Szalontay: Dr. van Vuurden: Neuropharmacologists will be important to predict brain pharmacokinetics, and they plan to implement immunotherapy combination treatments to promote an abscopal effect in the brain.

Dr. Packer: The future of DIPG treatment will likely be combination therapy; immunotherapy seems promising at this time. Future studies will require tumor biopsy to allow for targeted treatment.

4 Question to all

How will the field move forward to personalize treatment?

Dr. Nazarian: Several drugs are effective in preclinical studies but do not cross the BBB, and it would be interesting to look at some of these agents in combination with FUS.

.

Keynote Speaker

Bob Smith

Senior Vice President
Global Gene Therapy Business, Pfizer



Bob Smith

Senior Vice President
Global Gene Therapy Business,
Pfizer



View on the Foundation's
[YouTube channel](#) >

An accomplished biopharmaceutical executive with over 30 years' experience, Bob Smith leads Pfizer's Gene Therapy and Rare Disease portfolio from a strategic development and operational implementation perspective.

Pfizer aims to be the industry leader in gene therapy and has been investing in the field since 2014 with the view that the technology could be broadly applicable to patients with genetically defined diseases. There are more than 7,000 rare diseases; of those, more than 80% have a genetic etiology and about half of them primarily affect infants and children, unfortunately carrying significant morbidity and early mortality. Gene therapy has the potential to deliver transformational clinical benefits by changing the course of the underlying genetic etiology of the disease. With a broad portfolio of more than 20 preclinical programs, Pfizer also has three programs in early clinical development and three programs in phase 3 development. The company is expanding its gene therapy platform beyond traditional gene addition (using viral-mediated vectors) to more advanced second- and third-generation gene and base editing technologies.

FUS may provide solutions to various gene therapy delivery challenges, which include delivering the right dosage of genes into the right tissues and the right cell types within that tissue. The technology has the potential to improve the delivery of viral-mediated gene therapies and enable the use of nanoparticles that encapsulate a gene of interest and deliver it to specific cells within a specific tissue at the right dose. It is exciting that FUS provides a new and novel way to noninvasively deliver drugs and other pharmaceutical agents precisely to focal points within the body in a very high concentration. The use of FUS could also decrease systemic side effects and other toxicities involved in traditional gene delivery approaches.

Using FUS to reversibly open the blood-brain barrier could address a significant challenge in delivering gene therapies and other genetic therapies in central nervous system disorders. FUS can also enhance the permeability of stroma and other tissues, such as in the pancreas, where it has been difficult to achieve good clinical benefits. In addition, FUS can enhance the permeability of cell membranes and activate the release of compounds from nanoparticles.

Partnerships between medical device manufacturers and academic teams developing new therapeutics are needed to create products of interest to the pharmaceutical industry. Collectively, the field must prioritize which clinical indications would be worthy of partnerships between academic groups, medical device manufacturers, and potential biotech and pharmaceutical companies. Companies like Pfizer are interested in developing drugs that treat certain types of diseases and those that will deliver transformational benefits that

change patients' lives. Pharmaceutical companies invest in new technologies that fit within their long-term, strategic vision. The investment timeline cannot be decades, but it should allow for an appropriate amount of research and clinical development. The new technology must have a sound regulatory strategy and a solid, multistage clinical trial plan that is based on strong preclinical data and a positive risk-benefit profile for patients in need. The new product must then be deliverable through the pharmaceutical company's manufacturing and commercial distribution infrastructures.

To mitigate risk for the investing pharmaceutical company, its executives evaluate the cost of failure versus the potential benefit of having a product successfully navigate the research and development continuum and ultimately benefit patients. These executives are also interested in the intangible aspects of a new technology, such as attracting the appropriate level of scientific expertise to build relationships with the key opinion leaders and patient communities that may be impacted by the diseases. Pharmaceutical companies conduct scientific and technical due diligence to determine whether a technology could be complementary or synergistic with its overall therapeutic portfolio. They need a high degree of confidence that they can deliver a product that will benefit patients and the overall health care system.

Dr. Smith welcomed people to contact him to learn more about Pfizer's gene therapy program or inquire about potential collaborations.

.....

Liquid Biopsy for Brain Tumors

MODERATOR

Stephen Bagley, University of Pennsylvania

PANELISTS

Hong Chen, Washington University in St. Louis

Lauren Leiman, BLOODPAC

Ying Meng, University of Toronto

Patrick Wen, Dana Farber Cancer Institute

Graeme Woodworth, University of Maryland



Stephen Bagley, MD, MSCE

Assistant Professor of Medicine
University of Pennsylvania



View on the Foundation's
[YouTube channel](#) >

Dr. Bagley gave an overview of the urgent and unmet clinical need for liquid biopsy in GBM treatment. GBM is a fatal cancer with a median overall survival (OS) of 12 to 15 months despite aggressive therapy. He discussed common analytes of liquid biopsies for cancer, including circulating tumor cells (CTC), cfDNA, ctDNA, and extracellular vesicles.

Typical liquid biopsy, such as collecting plasma-based next-generation sequencing (NGS), showed limited clinical utility in GBM due to the blood-brain barrier (BBB). ctDNA is detectable in less than 10% of patients with gliomas compared with more than 75% of patients with other solid tumors. Such traditional liquid biopsy methods record no match between mutations in plasma and those from tissue in newly diagnosed GBM. Highly concentrated ctDNA-based liquid biopsy of CSF may be an effective way to characterize and monitor brain cancer.

The discussion tackled the promising role of FUS-enhanced liquid biopsy, which proved the ability to disrupt the BBB through enhancing the release of brain tumor biomarkers. Dr. Bagley highlighted the work of Dr. Meng et al., which showed that MRgFUS can safely and transiently open the BBB, providing circulation and enriched signal of brain-derived biomarkers in human patients with GBM.

Dr. Chen and colleagues' publication focuses on sonobiopsy for minimally invasive, spatiotemporally controlled, and sensitive molecular characterization of brain cancer. In a pig GBM model, this technique facilitated the detection of brain-tumor-specific mutations. Ongoing human clinical trials led by Dr. Woodworth are studying FUS-enhanced liquid biopsy as a noninvasive method to improve the care of patients with brain tumors.

Dr. Chen discussed the key milestones in sonobiopsy, a method developed by her team that uses FUS to target tumors deep in the brain. The method was first verified in 2018 through a feasibility study in mice, a safety evaluation study, and a study in pigs that showed improved brain tumor biomarker detection sensitivity. An IRB approval was granted in 2022 for clinical trials.

Dr. Wen highlighted the potential uses of liquid biopsy, including establishing a diagnosis and monitoring tumor relapse. Liquid biopsy may be beneficial in disease course monitoring to differentiate progression from pseudoprogression. It might detect potentially targetable genetic alterations missed by tissue sequencing.

Dr. Meng summarized the results of the first-in-human proof-of-concept study investigating MRgFUS and adjuvant temozolomide in patients with GBM. A multicenter controlled study is ongoing that explores the use of MRgFUS prior to surgery in newly diagnosed GBM. Finally, the immunomodulatory capacity of glioma-derived extracellular vesicles is a promising area of research. FUS increases release of such analytes.

Dr. Woodworth recognized the significance of blood and CSF sampling pre- and post-FUS treatment. Liquid biopsy analytes can be time specific; therefore the ability to detect them will depend on when the blood is sampled. For example, early clinical study protocols included patient blood sampling right before FUS treatment, at 30 minutes, 60 minutes, and 24 hours post-FUS for each cycle of treatment. It will be valuable to generate a repository of samples from clinical trials to support identification and validation of key analytes. A closer analysis of such components can improve the understanding of tumor biology and heterogeneity and pave the way to a more tailored care for patients with gliomas.

Ms. Leiman explained BLOODPAC's strategies to accelerate the development, approval, and accessibility of liquid biopsy. BLOODPAC and FUSF can establish effective collaborations across institutions to create standards and set trial design and clinical variables to support multicenter adult and pediatric clinical trials.

1 Question to Dr. Wen

If FUS is ultimately shown to have high sensitivity and specificity for detecting the most common mutations in the blood of patients with brain cancers such as GBM, how should FUS-enabled liquid biopsy be integrated into the routine care of these patients?

This could be useful throughout the life of patients. The challenge is to advance effective diagnostics and therapeutics and is due to the presence of the BBB, substantial intertumoral and intratumoral heterogeneity, and challenges in radiomics. Identifying reliable biomarkers and driver mutations for glioma could aid in tumor subtyping, development of targeted therapies, measurement of response to therapy, and differentiation of disease progression from pseudoprogression. For example, one has to compare differences between a tumor at diagnosis and at recurrence. Epidermal growth factor receptor (EGFR) variant III (EGFRvIII) expression is spontaneously lost in 50% of GBMs upon recurrence. FUS-enhanced liquid biopsy would help in detecting the driver mutations at time of recurrence.

2 Question to Dr. Woodworth

Biomarker evaluation in DIPG is difficult. Can you explain how you will address this?

The field is rapidly evolving, particularly with the recent findings on extracellular vesicles or new assays for fragmentomics. We need to understand the correlation between such analytes and tumor biology and their potential clinical applications.

3 Question to Dr. Meng

If FUS successfully opens the blood-brain barrier, will that alone provide high enough sensitivity and specificity for FUS-enabled liquid biopsy to be used clinically? If not, what are the other barriers?

The volume of BBB opening affects the amount of released ctDNA. The extent of secreted ctDNA in a patient's blood is closely correlated with the time of blood sampling from BBB opening, patient's tumor burden, and sample handling and storage. Thus, consistency should be applied in clinical trials with regard to applying FUS-enabled liquid biopsy techniques and the timing of sample collection.

4 Question to all

How soon after sonobiopsy should the blood sample be taken?

Dr. Chen: The number one question is when to collect the blood sample. Building on preliminary animal studies, the release of biomarkers is enhanced when blood samples are collected immediately at first time point after sonobiopsy treatment, and then later at different time points.

5 Question to Ms. Leiman

How could we eventually go about comparing results of FUS-enabled liquid biopsy using different FUS platforms (MRI-guided vs. implanted vs. neuro-navigation-guided)?

This is the specialty of BLOODPAC. Bringing together diverse stakeholders through FUS helps us understand the needs. The main project focuses on identifying pre-analytical clinical variables and creating standardization. Second, after data aggregation, submitting the project through FUS companies will help educate liquid biopsy stakeholders and move through the process. Third, increased access to data will support constant communication to develop standards and guidance for the liquid biopsy community.

6 Question to Dr. Wen

What is the optimal study design to definitively determine whether there is clinical utility to FUS-enabled liquid biopsy for brain tumors?

For most brain cancers, it is safe to collect samples from the CSF. Although not routinely used, it would be imperative to incorporate more CSF collection studies into trials, similar to studies used in systemic cancers trials.



Seated, left to right

Stephen Bagley, MD, MSCE

Graeme Woodworth, MD

Ying Meng, MD

Hong Chen, PhD

On monitor, left to right

Lauren Leiman

Patrick Wen, MD

7 Question to Dr. Chen

Is there a role for FUS-enabled liquid biopsy using CSF instead of or in addition to blood?

We do not have a concrete answer yet as we are performing preliminary animal studies in mice. Results are encouraging for FUS-enhanced biomarker release into the CSF.

8 Questions to all

Is there any development in the downstream analysis of liquid biopsy assays using machine learning or complex regression algorithms to help detection of biomarkers?

Dr Meng: I think that is the goal. However, part of the challenge is that blood sampling size is too low to yield sufficient statistical algorithmic analysis. Second, the absence of tumor tissue collection as a comparator in the first preliminary studies' inclusion criteria remains a limiting factor.

Dr. Bagley: In the routine practice for solid tumors, de novo mutation detection at diagnosis can be identified by liquid biopsy. Also, variation in key driver mutation concentration can be as well measured at the time of radiographic progression. Conversely, the lack of key driver mutation in brain tumors makes it more challenging, and researchers rely on the measurement of multiple common mutations at time of disease progression.

How close to the tumor on imaging should the sonication be for optimizing ctDNA yield?

Dr. Chen: One of the strengths of sonobiopsy is its ability to target a specific tumor area spatially and noninvasively and perform molecular targeted analysis at this precise region.

Dr Meng: Questions arise about the inevitability of BBB opening for sonobiopsy to be effective.

Dr Chen: Incorporating other modalities like hyperthermia along with BBB opening might enhance biomarkers release.

10 Question to Dr. Woodworth

According to your experience, how should FUS-enhanced liquid biopsy be integrated as a therapeutic modality into the routine care of patients at advanced disease stages?

Currently, strategies are directed toward incorporating FUS as a routine component of the recommended disease imaging and monitoring. Blood sample collection pre- and post-FUS can generate a deeper structural and functional knowledge of the disease state. Evolution of frameless MRgFUS has made the procedure less painful and has reduced time for procedure to around 20 minutes for a localized tumor focal point.

• • • • •

Sonodynamic Therapy

MODERATOR

Francesco Prada, Istituto Neurologico C. Besta

PANELISTS

Delaney Fisher, University of Virginia

Kismet Hossain-Ibrahim, University of Dundee

Chiungyin Huang, Chang Gung Memorial Hospital

Ko-Ting Chen, Chang Gung Memorial Hospital

Nader Sanai, Barrow Brain and Spine

Eleanor Stride, University of Oxford



Francesco Prada, MD

Neurosurgeon
Istituto Neurologico C. Besta



View on the Foundation's
[YouTube channel](#) >

Dr. Prada presented a concise definition of sensitizer-mediated therapies. Sonodynamic therapy (SDT) consists of systemic delivery of nontoxic chemical compounds called sonosensitizers. These compounds accumulate selectively in tumor cells or surroundings and then get activated by exposure to a form of energy. Typically, low-frequency ultrasound converts sensitizers to become cytotoxic agents and specifically destroy tumor cells without damage to adjacent healthy tissue.

The effectiveness and feasibility of SDT are impacted by the combination of frequency, intensity, duty cycle, and ultrasound application time. The limited permeability of the BBB and the short penetration depth of light prevent conventional photosensitizers from entering the CNS. Potential mechanisms of action of SDT include the generation of reactive oxygen species (ROS), the physical destabilization of cell membrane, and ultrasonic cavitation.

Dr. Prada discussed panelists' experimental setups for evaluating potential SDT bioeffects. Preclinical in vitro work by Hossain-Ibrahim et al. showed that ROS are a trigger for mitochondrial apoptosis pathways and cytotoxic effects of SDT. In a tumor xenograft mouse model, SDT was found to suppress tumor growth and inhibit expression of vascular endothelial growth factor in tumorous cells. SDT elicits immunogenic cell death and tumor immune microenvironment modulation.

Dr. Stride cited studies she collaborated in that focus on magnetic microbubble mediated chemo-SDT using a combined magnetic-acoustic device for the neoadjuvant treatment of pancreatic adenocarcinoma. Many drugs, including 5-aminolevulinic acid (ALA), porphyrin-based molecules, or xanthene dyes have been used as sonosensitizers. When metabolized, 5-ALA selectively accumulates in glioma tumor cells and can induce tumor regression upon sound activation. Conversely, fluorescein distributes well into the interstitial space. This selective extravasation in the ruptured BBB suggests attractive tumoral epifluorescence and tumor-specificity of the treatment.

Additionally, **Dr. Huang**'s in vitro and in vivo work suggests that the combination of FUS and 5-ALA may reduce glioma cell growth.

Interestingly, applications of FUS in cerebrovascular neurology are also being explored. For example, **Ms. Fisher**'s research relates to cerebral cavernous malformation. Employing 5-ALA and fluorescein with low-intensity focused ultrasound (LIFU) has shown good biosafety and remarkable efficiency. Current research and future directions should be focused on the advancement of SDT-based combination methods for the management of brain tumors.

1 Question to Dr. Stride

Based on your extensive research, what are the latest observations on the elicited mechanisms of action of sonodynamic therapy?

A lot is yet to be understood. We were able to produce sonoluminescence predominantly with microbubbles excited at low frequencies. However, the intensity of the light generated by sonoluminescence is obviously insubstantial for practical purposes. Efficient intracellular uptake and low efflux are vital to facilitate SDT effects. Currently, combination fluorescent-based approaches are being studied for better drug distribution, intracellular uptake, and activation.

2 Question to Dr. Hossain-Ibrahim

What are the effects of reactive oxygen species production in preclinical studies?

Based on our experience in photodynamic therapy, efforts emphasize measuring fluorescence produced through high multispectrum analysis. In fact, the ultrasound parameters used in published studies lack consistency. Under low sound pressure, bubbles show stable cavitation, but the ideal amount of energy is yet to be determined. Extensive clinical research is needed to optimize ultrasound parameters such as frequency, intensity, treatment duration, and mechanical index.

3 Question to Dr. Hossain-Ibrahim

Is cavitation being detected during sonication?

Here, we developed a system in conjunction with the fluorescent drug to support cavitation detection. To date, cavitation is not yet reported while pointing three levels of fluorescence energy; 200, 400, and 800 J.

4 Question to all

What are the ideal FUS parameters for SDT?

Ms. Fisher: The delicate hemorrhagic nature of cerebral cavernous malformation dictates the application of low-power intensity. Currently, our research is leveraging a power intensity of 2 watt/cm² and we will probably escalate the intensities as we progress with outcomes.

Dr. Stride: Interestingly, therapeutic effects did not occur in control groups with the absence of cavitation, in both in vitro and animal models. Frequencies as low as 0.5 MHz seem to cause little cavitation and more SDT effects. When increasing amplitudes, more effects are gained, but eventually this can lead to a violent collapse and destruction of the bubbles. There seems to be an optimal duty cycle and pulse duration. These findings are consistent between in vitro and in vivo studies. Upcoming challenges include obtaining a deeper knowledge and efficient methods to handle and sustain cavitation.

Dr. Sanai: In the phase 0/1, first-in-human, open-label study that we are conducting, safety and efficacy of ascending energy doses of SDT combined with intravenous (IV) 5-ALA are assessed in patients with recurrent high-grade gliomas. FUS treatment is administered approximately 4 hours after receiving the IV drug prior to the planned tumor resection. The drug dose for the first phase is 10mg/kg of IV 5-ALA. In every participant, half of the tumor volume is not targeted with for SDT and serves as a control.

The energy levels range from 200 to 400 to 800 J. Patient tumor tissue is assessed for sonodynamic and pharmacodynamic effects. Implementation of various pharmacokinetic techniques to measure ROS at the three different energy levels yielded statistical difference in the treatment arm versus control group.

Similarly, statistically different levels of tumor cell death were noted in treatment versus control group. However, radiographic evidence of tumor physiological imaging changes associated with SDT was not exhibited, unlike effects seen in preclinical models.

What are the benefits of IV 5-ALA versus oral? Is there a true difference? Does this need to be studied?

Dr. Sanai: Comparable plasma porphyrin 9 sensitization kinetics profile was noticed following orally and parenterally administered 5-ALA.

Dr. Hossain-Ibrahim: While the IV formulation is hypothesized to have less hepatotoxicity, the oral administration of 5-ALA remains simpler, safer, and more acceptable to patients.

Dr. Prada: We are administering the commercially available oral formulation of 5-ALA in Milan.

Besides 5-ALA, are there other sonosensitizers that we should urgently bring to the clinic? For what tumor types?

Dr. Huang: We applied both fluorescein and 5-ALA in animal models and found comparable effects. Nonetheless, their effects should be assessed in human clinical trials.

Ms. Fisher: Incident binding of tozuleristide chlorotoxin peptide to cerebral cavernous malformation deserves further investigation for its application in cerebrovascular diseases. Fluorescein does not seem to accumulate in vascular lesions.

5 Question to Dr. Chen

How do you deliver FUS?

Our treatment strategy is based on the use of nanobubbles for their attractive use in recurrent tumors. In conjunction with microbubbles, propylene oxide (PPO)-based nanobubbles carry a mechanism to trigger drug release and improve therapeutic delivery. Strategies should be directed toward increasing the efficiency of nanosized delivery vehicles in recurrent tumors.

6 Question to Dr. Hossain-Ibrahim

Can different power waves elicit different amounts of bioeffects?

The amount of energy absorbed by the tissues essentially estimates the bioeffects of SDT. Accordingly, the treatment decision should be clear whether to target the whole brain, the entire neoplasm, or successive small regions. The amount of SDT bioeffects can vary based on the insonating beam (targeted or unfocused). Immunohistological evaluation should inspect SDT bioeffect on both central and peripheral areas of targeted tumor tissues.

7 Question to Dr. Sanai

Is FUS truly needed, or is unfocused, whole organ ultrasound ideal? Can you achieve enough power if it is "less focused"?

Owing to its deep tissue penetration, FUS would be better in inducing key cytotoxicity at deep-seated tumor sites. However, its therapeutic efficacy can be compromised due to large tumor volume, consequent long duration of treatment, and asymmetrical characteristics of the tumor. Current limitations in SDT equipment and software can hinder the eradication of tumor cells at a deeper tissue level.

8 Question to Dr. Stride

According to your experience, what area do you target in other solid tumors?

The nature of tumor vascularity is studied among numerous solid tumors such as breast, prostate, and pancreas. Evidence shows a relationship between ROS production, sensitivity of the cells, distribution of the drug, and tumor vascularity. Heterogenic vascularity is a very significant consideration and can offer new perspectives on a drug delivery system.

9 Question to Dr. Stride

Is the cavitation component of SDT considered an enhancer of drug penetration, distribution, and/or activation?

It could be all the above. Enhanced drug penetration is seen. Undoubtedly, certain drugs show intracellular toxicity even in the absence of ROS. In terms of clinical utility, the difference between extra- and intracellular toxicity is not hindering benefit from therapy.

10 Question to Dr. Stride

What is the effect of encapsulation and the effect of adding microbubbles to potentiate or enhance SDT?

Research suggests that the combination of drug-loaded microbubbles and ultrasound possess enormous advantages in brain tumor penetration. Preliminary studies suggest the potential that oxygen-loaded microbubbles may enhance SDT. The stability and applicability need to be researched.

11 Question to Dr. Huang

Are you considering combining microbubbles and SDT in clinical trials?

The combination of oxygen-carrying microbubbles with sonosensitizers provides enhanced sonodynamic activation at the treated site.

12 Questions to all

How do we measure the effectiveness of SDT? Is it safe?

Ms. Fisher: I do not have a clear answer to this question since most of our experience is centered on the BBB opening approaches. Nevertheless, an imperative milestone would be to observe the long-term chronic effects and outcomes of SDT.

Dr. Sanai: The outcome measures should be as specific as possible. Unbound drug concentrations should be collected from conventionally non-enhanced tumor tissue samples. Radiographic evidence of tumor physiological changes associated with tumor cell death should be interpreted. The histology shows SDT's tumor-killing effect, but the magnitude of effect does not have clinical relevance with the existing approaches.

Dr. Stride agreed that outcome measures should be defined in human clinical trials.

Do diverse sonosensitizers affect cell apoptosis differently?

If yes, does this affect the innate immune or molecular response after treatment?

Dr Prada: In my in vivo experience on mice, there was not a big difference between 5-ALA and fluorescein in terms of immune response.

Dr. Stride: It is consistent with our findings as well.

.

Chronic Pain

MODERATOR

Dheeraj Gandhi, University of Maryland School of Medicine

PANELISTS

Abdul-Kareem Ahmed, University of Maryland, Neurosurgery

Brian Dalm, The Ohio State University Wexner Medical Center

Min Gon Kim, Carnegie Mellon University

Erica McCune, Columbia University

Shayan Moosa, University of Virginia

The panel discussed FUS approaches to treating various chronic pain indications, including central and peripheral neuropathies, and explored future directions for the field.

Dr. Gandhi introduced the panel and gave brief summaries of their work.

- **Dr. Ahmed** works with Dr. Gandhi to study bilateral MRgFUS central lateral thalamotomy for refractory trigeminal neuralgia and refractory neuropathic pain.
- **Dr. Dalm** is studying cingulate gyrus access with FUS for relief of chronic pain from malignancies. With more superior and anterior positioning of the frame, the site for cingulotomy was moved farther within the treatment area, allowing for accurate targeting and heating of the cingulate gyrus was accomplished in a cadaver model.
- **Dr. Kim** is studying how low-intensity focused ultrasound (LIFU) may modulate pain in animal models. Recent findings showed that a single session of LIFU at specific pain-processing circuits resulted in significant changes in pain-related behaviors in mice.
- **Ms. McCune** has studied median nerve FUS neuromodulation to reduce somatosensation in healthy volunteers and is now studying the technique in patients with carpal tunnel syndrome. She is also looking at peripheral FUS neuromodulation to decrease mechanically induced neuropathic pain.
- **Dr. Moosa** led a randomized controlled trial of 10 patients using bilateral MRgFUS medial thalamotomy for trigeminal neuropathy.



View on the Foundation's
[YouTube channel](#) >

1 Question to Dr. Kim

Please describe your study design. How do you differentiate between stimulatory and inhibitory signals, and how did you choose those parameters?

We conducted preclinical studies to quantitatively evaluate the effect of LIFU on pain-associated behaviors in wild-type mice and well-established humanized sickle mice. Targeting the primary somatosensory cortex resulted in significantly reduced pain or hip pain sensitivity in male and female mice. We compared the withdrawal response of ipsilateral and contralateral reactions; based on calculated values, we determined excitatory or inhibitory signals.

2 Questions to Ms. McCune

Please describe your study design. How long is the treatment in a particular patient? What did you observe?

In the carpal tunnel study, we applied electrical stimulation to the wrist of patients to induce a thumb twitch. We then applied FUS upstream in the forearm, targeting the median nerve using displacement imaging. An EEG cap was placed on the subjects to record the evoked potentials induced with electrical stimulation. We are doing 1,000 electric pulses; half are paired with FUS. So far, in both healthy subjects and patients, we have observed reductions in the amplitude of the somatosensory signal recorded in the EEG, with larger reductions observed at the higher pressure compared with the lower. The actual sonication time is about 17 minutes. The entire procedure takes about an hour.

Going forward, how would we determine the kind of patients who might benefit from central versus peripheral neuromodulation?

Whether you choose a central or peripheral sonication scheme depends on the type of neuropathy being treated. Patients enrolling in the peripheral studies have pathologies associated with a peripheral nerve, such as carpal tunnel syndrome associated with median nerve compression. When the neuropathy is in the peripheral nerve, it makes sense to directly sonicate that area.

What is the duration of therapy and how often would these neuromodulation therapies be applied to gain meaningful chronic relief from pain?

The next step in our study is to investigate the longitudinal effects. We had one patient who reported being able to move her arm more freely without pain 3 days after treatment. We need to investigate the parameters that will be effective in long-term pain reduction.

3 Questions to Dr. Dalm

Please explain your choice of target for your particular study. What challenges did you face to produce a lesion in the cingulate gyrus?

We specifically targeted cancer-associated pain. About 70% of patients have a meaningful pain response to radiofrequency (RF) and laser ablation. We were looking at more



Left to right

Dheeraj Gandhi, MBBS

Min Gon Kim

Erica McCune

Brain Dalm, MD

Shayan Moosa, MD

Abdul-Kareem Ahmed, MD

noninvasive options to treat these patients by using FUS to try to replicate past successful treatments. As far as challenges in producing a lesion, we worked with a fresh frozen cadaver that had a large parietal brain tumor and edema displacing the area to access. Frame placement was probably the most challenging, along with placement of pins to avoid rupturing the membrane.

We faced challenges in patients with trigeminal neuralgia who had had microvascular decompression (MVD) in the past, with fewer elements available for treatment.

How many elements were available for your treatment?

We had about 800. We had to deal with membrane fold issues. Even with altered frame placement, access to the target for proper heating was still challenging.

Do you foresee any safety issues as you move into the clinical realm?

Depending on the number of treatments needed, general anesthesia or deep sedation would be safer for the patient, given that they have end-stage cancer and have already endured multiple other treatments. Temperatures that we achieved in the cadaver studies could potentially be high and intolerable over a long treatment time.

4 Questions to Dr. Moosa

Please briefly describe your study design. What kind of patients did you enroll in your trial?

We completed a randomized double-blind study of 10 patients with chronic medication-refractory trigeminal neuropathic pain. We performed a bilateral medial thalamotomy, specifically targeting the posterior aspect of the central lateral nucleus of the thalamus. Three months after the procedure, we saw no significant change in pain scores and imaging markers. The Maryland trial studied patients with trigeminal neuralgia, which is an intermittent pain study. Ours looked at constant pain. Other options for chronic constant neuropathic pain may be the use of neuromodulation or ablative therapies at other targets.

Did you have any patients that were difficult to lesion or could not tolerate frame placement?

We did not have too much difficulty in terms of achieving heating, but patients with chronic pain are much more likely to be sensitive to painful stimulation, such as that experienced with a frame and being in a scanner for hours.

10 Question to Dr. Ahmed

Would you share your analysis of chronic versus episodic pain?

We recently completed a single arm trial on the use of bilateral FUS central lateral thalamotomy for refractory neuropathic pain and are following that with a single arm trial of the same procedure for refractory trigeminal neuralgia. In the neuropathic pain trial, patients with episodic pain or allodynia had significantly greater improvement than those with continuous pain (80% vs. 20%). So classic trigeminal neuralgia is actually well suited to the procedure because of its episodic nature. It is a very serious disease, often called the “suicide disease” for how it affects people. Most patients with classic trigeminal neuralgia have a vessel loop that impinges the artery. A book, *Working in a Very Small Place*, describes it well.

11 Questions to all

Please comment on how you chose the tools or questionnaires for your particular studies.

Dr. Moosa: We used the Numerical Pain Rating Scale (NPRS), as well as patient-reported outcome measures and the Patient Global Impression of Change (PGIC), which are all commonly used in the literature. However, pain is multifaceted and involves a matrix

Left to right

Min Gon Kim and
Erica McCune



of sensory, affective, emotional, cognitive, and even motor components. Moving forward, we need to be able to tease out the components of pain that may change with the techniques we use. Our study did not look at affective components.

Dr. Ahmed: We used specific scales that looked at how pain affects peoples' lives, i.e., the ability to eat, sleep, and enjoy themselves. This put the onus on us to ensure that the intervention had a meaningful effect. Many prior studies used the Visual Analog Scale (VAS), which is well studied but static and not suited to neuropathic pain.

Dr. Gandhi: One of the drawbacks of some previous studies is their use of the VAS, which is not a validated scale for neuropathic pain.

Do you see a path forward for using neuromodulation as a predictive tool for patient selection for either ablative or other central nervous system procedures?

Dr. Kim: We will need to select suitable brain target regions, based on measurements with functional MRI (fMRI) or EEG to assess brain activity and connectivity, and use a suitable dose of stimulation. We may want to target specific neuron types for suppressing pain.

Ms. McCune: These procedures seem to be effective in patients with episodic pain. Our studies involve patients with chronic neuropathies, but we are also looking at more acutely induced pain. It would be interesting to see if these neuromodulatory procedures would reduce pain induced in these specific pathologies.

Do you think this technology could evolve enough in the next few years to become a viable option for, say, a patient with carpal tunnel syndrome that is resistant to other therapies? With a wearable transducer, maybe?

Ms. McCune: One of the large barriers with wearable devices is the requirement for high pressures, i.e., 1.6 to 2.5 megapascals and higher. If we were able to overcome these issues, a wearable device would be interesting to explore for continuous sonication.

Do you feel that that deep brain stimulation (DBS) might be attractive as an FUS target in the future as well as for ablative lesions?

Dr. Moosa: We studied anterior insula stimulation in patients with epilepsy who had EEG electrodes placed to map seizure focus. We stimulated this area in six patients and saw a huge jump in the amount of heat pain that they were able to tolerate. We are planning a clinical trial of DBS in the anterior insula in patients with chronic intractable neuropathic pain. Other studies are showing that this is possible.

What might you see as a clinical path moving forward for using cingulotomy FUS in terms of trial design with this vulnerable population?

Dr. Dalm: We would like to replicate the results in more cadavers before implementing it in living humans, just to ensure that the procedure is feasible 100% of the time and that we know all of the maneuvers and elements available to us. The trial design is tricky. These are not patients that we would want to randomize to a sham procedure. I envision

doing a limited trial of five or six patients before expanding. Initially, our thought is to prove that the results are reproducible.

How can we decouple clinical pain relief from reduced somatic sensation or desensitization? In targeting a certain area, how can you tell whether you are treating the pain rather than just reducing the sensation of the circuits?

Dr. Ahmed: Clinically, there is a difference. With some of these targets, we are modulating a circuit that we call the “pain neuromatrix.” There are different nodes in this circuit that would still allow the sensation of normal stimuli, such as heat, cold, and touch, and not cut off all sensation, as in procedures used 50 years ago.

Dr. Moosa: We tested heat pain thresholds in patients receiving anterior insula stimulation. Patients reported feeling the pain sensation but not caring about it; the emotional aspect was removed. As we learn more about the pain matrix, we will be able to tease out the different aspects in future studies and address all components of the pain matrix in our outcome scales.

My biggest concern with high-intensity focused ultrasound is the volume of tissue to be ablated. If patients are put under general anesthesia during the procedure, do we know what kind of damage can happen with skull heating? Is it a benign phenomenon, or are we concerned about actual injury if we start to look at multiple 30 kilojoule sonications?

Dr. Dalm: There is no standardized way to look at this. Extremes of energy delivery need to be considered potentially dangerous since the patient will not be able to give feedback under general anesthesia. I have not seen a burn yet at the levels we are using.

Dr. Gandhi: I have only one related patient experience to share. This patient had bilateral MVDs and a small head, with only about 700 to 800 elements to work with. On day one, the patient had a small area of edema in the cerebellum, removed from the thalamotomy location. They were asymptomatic and the edema disappeared on follow-up, and this may have had something to do with the high energy levels we used.

.

Veterinary

MODERATOR

Nikolaos Dervisis, Virginia-Maryland College of Veterinary Medicine

PANELISTS

Shawna Klahn, Virginia-Maryland College of Veterinary Medicine

Adam Maxwell, University of Washington

Ramasamy Paulmurugan, Stanford University

Ashish Ranjan, Oklahoma State University

Joanne Tuohy, Virginia-Maryland College of Veterinary Medicine

The panel discussed veterinary medicine's role in advancing the field of FUS and the hurdles and limitations to overcome in order to increase adoption of the technology.

Dr. Dervisis introduced himself and the panelists and briefly summarized their work.

- **Dr. Dervisis** has studied the feasibility of targeting canine soft tissue sarcoma with ultrasound-guided HIFU and monitored the tumor microenvironment for changes that occur after treatment.
- **Dr. Klahn**'s work involves histotripsy and use of nonthermal, mechanical tumor ablation in dogs with soft tissue sarcoma, with a specific focus on the immunomodulatory capacity of FUS.
- **Dr. Tuohy** has focused on osteosarcoma in dogs and is studying histotripsy to ablate the primary tumor, with the goals of treating metastatic disease as well as the primary tumor. Her team is also assessing the treatment's immunomodulatory responses within the tumor and peripheral circulating immune cells.
- **Dr. Maxwell** is conducting research on burst wave lithotripsy, which uses FUS to break down kidney stones in the ureters of cats. This technology was also recently used in two human feasibility trials.
- **Dr. Ranjan** is studying thermal ablation in dogs to induce remission of unresectable tumors by leveraging the immunomodulatory properties of HIFU to improve the anti-tumor immune response.
- **Dr. Paulmurugan** is using microRNA as a therapeutic agent to reprogram cancer cells and has shown that the use of ultrasound microbubble-mediated delivery can deliver a sufficient amount of microRNA to hepatocellular carcinoma in canine liver and can be used to follow chemotherapy.



View on the Foundation's
[YouTube channel](#) >

1 Questions to all

Please comment on how working with this new technology in animals can not only help advance the technology but also help people.

Dr. Ranjan: Pet patients share the same family life with humans and have similar pathophysiologies. Some tumor types such as melanoma and sarcoma have similar clinical presentations in both. A vet study can provide an opportunity to apply it to humans, either in sequence or parallel. I do not think the veterinary community intends to treat animals only to advance human medicine. The goal can be bilateral, where we advance veterinary medicine while also helping human clinicians understand the value of the veterinary trials, and vice versa.

Dr. Maxwell: One of our long-term interests is treating pediatric kidney stone disease, which has become more prevalent over the past couple of decades. To conduct a pediatric clinical trial with a new technology, additional data are needed on how the changes to a system will impact the smaller anatomy of a child versus an adult. Our data in veterinary trials will be directly applicable to understanding the scaling of the technology to conduct a clinical trial in children.

Dr. Tuohy: Pets have a shorter expected lifetime than humans, so outcomes of therapeutic treatments, including devices, can be assessed faster than in a human clinical trial. That is another advantage.

What do you see as a major hurdle in the development of FUS as a therapeutic modality in veterinary medicine?

Dr. Klahm: One of the major limitations, but also one of the benefits, of employing these technologies in veterinary patients is that the clinical presentation of the tumors is incredibly similar to those of humans, in terms of subtypes and tumor size. The downside is the time it takes to treat a large volume of tumor. A 3-cm ablation area could involve about an hour of anesthesia. We need a technology for rapid, large-volume ablation.

Dr. Paulmurugan: When we selected microRNA as our therapeutic, we noticed that the microRNA sequence is exactly similar to that of humans, even though the primary transcript is completely different. The trials in canine models can be used to translate into human trials. It is quite difficult to use the current ultrasound system for a large tumor area, so the technology needs to move forward to deliver therapy faster than with the current strategy. Systems will need to be adjusted to deliver energy just to the tumor without killing the normal tissue.

Dr. Maxwell: There is a lot of heterogeneity in the anatomy of dogs compared with humans. It is hard to design a single system to treat across the spectrum of anatomic presentations of animals. A number of components will need to be integrated into one system to treat at the larger end of the size range, especially for things like deep tumors or abdominal applications.



Left to right

Nikolaos Dervisis, DVM, PhD

Joanne Tuohy, DVM, PhD

Ashish Ranjan, BVSC, PhD

What is the biggest hurdle that you foresee in translating your research from animals into human clinical trials?

Dr. Ranjan: It depends on the indication treated. There are broad differences between how veterinarians and human oncologists view devices. For veterinarians, cost is a factor, so it is more challenging to develop a system for a vet patient. Hurdles can be mitigated to some extent if the indications are chosen appropriately. If the focus is on disease types with similar pathophysiological features, the hurdles may be less.

Dr. Tuohy: Another hurdle, which is not insurmountable, is in the realm of immune evaluations and having a robust data set that can be used to support human clinical trials. There is limited availability of canine-specific reagents for immune analysis, as well as limited availability of agents widely used in human patients, such as monoclonal antibodies.

• • • • •

FDA Town Hall

MODERATOR

Jessica Foley, Chief Scientific Officer and Managing Director, FUS

PANELISTS

Bennett Blumenkopf, Clinical Reviewer

Gregg Kittlesen, Scientific Project Manager

Subha Maruvada, Research Engineer

Matthew Myers, Research Physicist

Jenna Osborn, Scientific Manager

Devashish Shrivastava, Biomedical Engineer



Jessica Foley, PhD

Chief Scientific Officer
and Managing Director
Focused Ultrasound Foundation



View on the Foundation's
[YouTube channel](#) >

A panel of experts from the FDA addressed questions about the FDA's function and procedures. Although the panelists could not comment on specific submissions, attendees were encouraged to ask about their past interactions with the FDA or about the agency's pathways, programs, and processes.

1 Questions to all

When does it make sense to have a pre-submission meeting?

Dr. Kittlesen: In terms of timing, it is helpful to get in touch whenever someone is ready to engage on an important aspect that will guide them through the regulatory process. Being specific in submissions and questions leads to the most fruitful interactions.

Dr. Blumenkopf: From the clinical standpoint, the pre-submission begins a dialogue to address important issues about the investigative protocol, such as safety concerns, endpoints, and appropriate candidates. It is a way to build a foundational understanding. When the investigator is ready to submit the investigative protocol or investigational device exemption (IDE), it is easy sailing ahead. At the IDE stage, the FDA has very limited time constraints and can issue a disapproval if an issue cannot be quickly resolved.

What is the timeline for pre-submission in terms of the time it takes FDA to schedule and respond? How much time should investigators add to their timelines?

Dr. Kittlesen: The FDA has a guidance document that details the submission process. The FDA will supply written comments on the pre-submission in 70 days. If a meeting is requested, it is typically scheduled about 5 days after the comments are sent. Typically, within the first couple of weeks after the pre-submission, the pre-submission is assigned to a lead reviewer who will reach out to the sponsor to set a mutually agreeable date for a meeting.

Could you discuss the processes involved with combination products and how to resolve conflicts? Some companies have reported “getting stuck” between the Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER).

Dr. Kittlesen: The FDA issued a guidance document this year related to combination products. Basically, the FDA is always looking for the principal mechanism of action, so a very clear description, supported by the literature or test information, will provide guidance in determining the appropriate lead center.

Dr. Blumenkopf: Regarding FUS, it is not necessary to file both an IDE and an Investigational New Drug application (IND). Each center captures the salient concerns of safety and effectiveness. If the submission involves use of an on-label drug, it is submitted as a device. If an off-label or novel drug or biologic is involved, it will likely go to CDER.

Some investigators use a microbubble or other type of particle to either enhance FUS or to enable FUS to open a barrier, such as the blood-brain barrier. Is the bubble considered a drug or device? Or does that vary?

Dr. Kittlesen: Generally, if something is clearly acting in a structural context, it will be a device-led submission and pre-submissions would go to CDRH. If a particular substance has been regulated as a drug and will be used as a device, submission may not be as clear. It may be best to contact either agency by email to raise the question about a pre-submission.

In thinking about the future of FUS, which is evolving from just an ablative application to types with different mechanisms of actions, could comparisons to transcranial magnetic stimulation (TMS) or microwaves be deemed predicates? Do predicates always need to be the same energy source?

Dr. Shrivastava: If a device is considered to involve a significant risk, there is a good chance that it will become a Class 3 device. Questions should be raised with the FDA as early as possible to determine if the questions of safety and efficacy relate to Class 2 or 3. If there is a predicate or the device does not involve a significant risk, it will involve a 510(k) submission; a guidance is available for this.

Dr. Myers: There is a risk of mechanical damage associated with ultrasound that is not seen with other types of energy, such as electrical energy.

6 Does everything deemed “therapeutic” need to have a full FDA review? For example, some applications may have a very low intensity or pressure.

Dr. Blumenkopf: I encourage a study risk determination at a very preliminary stage as the best approach. Most IRBs are familiar with this. If a significant risk is determined, the application will need to go through the FDA regulatory process.

Dr. Myers: Neuromodulation will be an interesting consideration. Currently, the way that most neuromodulation studies are conducted involves a nonsignificant risk decision. But increasing the intensity of neuromodulation can have more subtle effects on, for example, inflammation and nerve function.

Are there any special considerations or additional information that study sponsors need to address for pediatric applications?

Dr. Blumenkopf: The process is similar to that for adult applications but will involve engagement with other FDA reviewers in pediatrics.

What is the FDA's thinking on rare diseases and accelerated approval processes or timelines?

Dr. Blumenkopf: The FDA has a humanitarian use designation and has had a couple of protocols submitted.

Dr. Kittleson: The FDA recently issued guidance information on the humanitarian device exemption, which may help accelerate the regulatory process for devices to treat individuals with rare diseases. “Humanitarian device exemption,” “expanded access,” and “breakthrough device program” are three key phrases that sponsors can address to advance their proposed devices to this market.

If a colleague and I have two different devices that both deliver the same amount of energy to the brain, and we are interested in device-independent risk determination, do you care more about the energy than the device?

Dr. Myers: The energy is definitely part of the consideration, but there are multiple other considerations, such as the targeting accuracy of the device, the total exposure, duration, and whether cavitation is monitored.

Dr. Blumenkopf: If the second device is ostensibly the same as one that has been already approved for use, that process may involve a 510(k). If the device is novel and has not been marketed, the question is whether it needs to go through an investigative protocol. This is where the study risk determination comes in.

Do you see a future redefinition of how much can be given as a clinically approved microbubble for use in opening the blood-brain barrier or coupled with a dynamic therapy to deliver more drug to a tumor? Dosing is currently limited to the maximum dose based on cardiovascular use.

Dr. Myers: The FDA does not have a guidance on this now but addresses it on a case-by-case basis. Many questions need to be addressed beyond the traditional thermal and mechanical damage criteria. For example, a better understanding is needed of the inflammatory response and the length of time the blood-brain barrier stays open.

What can we do as a community to help you answer some of these questions to get to the point of official guidance?

Dr. Maruvada: A great place to start would be to keep track of parameters being used and develop a consensus. Publishing them would be useful not just for the FDA, but for the field in general.

Dr. Myers: It would be helpful to catalogue where the field is now and where it wants to go.

Dr. Blumenkopf: I encourage investigators to use the public resources of the FDA as well. It would be helpful for the Foundation to add information to its website about CDRH and the FDA offices.

Dr. Kittlesen: Add links to the feasibility studies program at CDRH, and a guidance document that describes opportunities to engage with CDRH.

Please comment on the use of a combination of three drugs plus a device marketed for HIFU but not for sonodynamic therapy. Two of the drugs are already marketed; the third would be viewed as a functional excipient.

Dr. Blumenkopf: There are several aspects to the IDE regulations, including the physiological research, the nonsignificant risk studies, and different categories of exemptions to the regulations. The submission process would determine these.

The FDA provided the following links in this session:

- Program email
OSEL_therapeuticultrasound@fda.hhs.gov
- Use of computational methods in regulatory decision making
<https://www.fda.gov/media/87586/download>
- Early Feasibility Studies (EFS) Program
<https://www.fda.gov/medical-devices/investigational-device-exemption-ide/early-feasibility-studies-efs-program>
- Computational Modeling Guidance
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions>
- FDA Therapeutic Ultrasound Program Page
<https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/therapeutic-ultrasound-program-research-therapeutic-ultrasound-medical-devices>
- Nonsignificant risk and significant risk medical studies
<https://www.fda.gov/media/75459/download>
- Humanitarian Device Exemption (rare disease question)
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program>
- General Wellness Guidance for Low-risk Devices
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-wellness-policy-low-risk-devices>
- Principles of Premarket Pathways for Combination Products
<https://www.fda.gov/media/119958/download>
- Requests for Feedback and Meetings for Medical Device Submissions:
The Q-Submission Program: Guidance for Industry and Food and Drug Administration Staff
<https://www.fda.gov/media/114034/download>

• • • • •

Fireside Chat

Capital Markets

SPEAKER

Sumit Mukherjee, Bank of America Merrill Lynch

MODERATORS

Patrick Edelmann, Focused Ultrasound Foundation

Philip Keevil, Focused Ultrasound Foundation

Mr. Mukherjee answered the moderators' questions about the current state of capital markets in medical technology, given the trials and tribulations over the past year. He discussed the status of the public markets, the appetite for investment in medical technology, and alternative fundraising mechanisms that entrepreneurs may think about as they design their business models.

1 Can you provide an overview of what is going on in the markets right now?

It is very easy to turn on the news and get depressed about the state of the markets today, but there is a lot of hope and much we can learn from the past few years. Inflation is impacting the market and triggering the reaction by the Federal Reserve. For most of the past decade, we lived with an extremely low to zero interest rate, which made it easy for investors to take risks. Now, risk becomes more challenging, and investors must be much more differentiated in where they park their capital. Inflation rates, concerns about recession, the geopolitical landscape, the challenges with the supply chain and labor have led to indecisiveness and nervousness around parking capital. The healthcare and technology sectors were great beneficiaries of the bull market and valuations were driven to peak levels. But even as these valuations retract, enthusiasm still exists, and the market is forward-looking.

2 There is a saying that markets prices take the stairs up and the elevator down. We have seen that in the public markets. Have you seen that in the private markets yet?

Yes, some of the same disciplines employed by public market investors are being applied to private companies. The valuation comparables in the public markets have drastically changed and are starting to reset in the private market. Also, not being able to predict when the initial public offering (IPO) market will return to normal also plays a role in how investors think about their time horizons and investments, and the valuations they need to be compensated for before a company goes public.



View on the Foundation's
[YouTube channel >](#)



Left to right

Philip Keevil, Sumit Mukherjee,
and **Patrick Edelmann**

3 Healthcare started a downdraft in the middle of last year. Can you walk us through what happened and why? What changed in the investors' mindsets and where are we now?

The biotech index was the first to peak in February 2021, driven by the excitement around innovation. This impacted the traditional disciplines in the public market, which also started to expand. People became more willing to take risks and companies that historically would not have been able to go public did so as the market gained strength and momentum. Some of these companies were in preclinical stages and once they became public, there was a long gap before real data were obtained to support value. Investors started to sell those stocks aggressively and moved from a growth to a value orientation, with biotech taking the hit first. The rest of healthcare felt the impact toward the middle of 2021 and investors started focusing on the “flight to quality” aspect and saw greater safety and stability in large cap pharma and managed care.

4 It was surprising to see how poorly medtech had performed in the biotech index. Can you talk to that point?

Investors still have a significant interest in finding new ideas and new companies in the medical device area but are dealing with the challenges of the broader market and are slow to invest capital aggressively. In 2020 and 2021, there were 225 IPOs, with about \$60 billion raised. In 2022, there were only 10 healthcare IPOs. Many of the companies that went public in 2019 and 2020 are still trading at healthy multiples. There has not been any new company formation this year in the area of medical devices. As the downturn lingers, there are concerns around recession and the acknowledgment that the multiples achieved at the peak times were probably unrealistic. The private equity community has raised a lot of capital to invest, and I think the pendulum will swing back, with interest in dual path public combinations.

5 How are venture capitalists talking about medtech? Biotech and healthcare seem flush with cash but pulling someone into the medtech world is “like pulling teeth.”

With the IPO market not being as great a threat as earlier, some of the larger medical device companies are excited about opportunities and are challenged to find ways to drive revenue growth. Many device areas can fit as a complementary piece within their portfolios, and the larger companies are exploring relationships with small companies with innovative technologies. I would expect this to be a larger part of the landscape going into next year. For the larger companies, it is not just about the purchase price, but the capital needed once the smaller company is brought in-house.

Sumit Mukherjee



6 Are there any general themes (e.g., drug delivery, neuroscience) that resonate consistently with investors now?

Yes, there is a lot of excitement about neurology, cardiology, drug delivery, and drug discovery platforms, as well as in technologies like machine learning and AI. For devices, the most excitement is around the larger markets because there are established sales forces and room to grow.

7 Does the fact that about 100 more companies than average went public (in 2020 and 2021) imply that some of them should never have gone public?

The companies were able to find capital, but the challenge is that many did not have the infrastructure to be a public company. There is no margin for error. If missteps are made in the public market, together with an increasingly fragile backdrop, investors will have an easy excuse to sell and buy much cheaper later. But I think enthusiasm has not waned and we will start to see capital come back.

8 Are these smaller companies being properly followed? Can they become orphans in the market?

A number of things can contribute to smaller companies becoming orphaned, including their liquidity profile and the size and scale of the market. Equity research plays an important role in monitoring companies on a quarterly basis and helping investors understand what the company does.

9 U.S. healthcare markets constitute the largest market in the world. How important is the U.S. market plan to the rest of world?

The U.S. market continues to be one of the most relevant and important markets. Having a presence in the United States and being able to demonstrate growth within the United States is incredibly important.

10 Can you speak to the other avenues of capital-raising that might exist out there right now?

Creativity around accessing capital has definitely become more pronounced in our current environment. Venture debt is one option. Companies that are not making money are now putting debt on their balance sheet and need to confidently demonstrate that the revenue engine will continue to operate and grow in the near future. The scrutiny to take on venture debt needs to be high.

11 Please explain special purpose acquisition corporations (SPACs)—what they are and where they are going.

SPACs are blind pools of capital raised with the intent of acquiring a target company in a certain subsector. SPAC issuance peaked in 2020 and 2021 to the point of actually doubling the IPO market in the amount of capital raised. They became a viable alternative for private companies to go public. In healthcare, a number have become public across the services and medical device spaces, and many have suffered. We have learned that the shareholder base that brought in capital to raise the SPAC initially is

often not the one that would own the underlying company. The attempt to bring in capital this way has been met with skepticism. Much of the capital was in trust and ended up with redemption. Also, the research analyst does not have a role in the SPAC context, as with an IPO. SPAC issuance has declined precipitously.

12 Can you give us some optimism about where things are going from here?

Despite what we are hearing in the marketplace right now, I am very optimistic about what the future holds. The excitement and interest around innovation remains remarkably high, especially around healthcare, an area people recognize as one they must get right. A stable market backdrop will foster an environment in which people will begin to reinvest. We are already starting to see improvement in biotech, which started its downturn earlier than other healthcare subsectors. Companies with positive data readouts are being met with significant capital to fund their initiatives. I anticipate the same enthusiasm returning back to the medical device, tools, and diagnostic markets, and eventually back into the services market.

• • • • •

Wednesday, October 26, 2022



Wednesday,
October 26, 2022



Timothy Bullock, PhD
Associate Professor of Pathology
University of Virginia



View on the Foundation's
[YouTube channel](#) >

Cancer Immunotherapy— *Where are we now?*

MODERATOR

Timothy Bullock, University of Virginia

PANELISTS

Irving Allen, Virginia Tech

Katherine Ferrara, Stanford University

Joseph Frank, National Institutes of Health

Awndre Gamache, University of Virginia

Tatiana Khokhlova, University of Washington

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

Dr. Bullock briefed the audience on the current state of research. FUS has recently advanced as an immunomodulator of the tumor microenvironment. Considerations of regimens, methods of application, and barriers to use of FUS should be reviewed along with future clinical applications.

Dr. Bullock broke down FUS immunogenicity pathways in tumor cells. In the cancer immunity cycle, FUS can first escalate tumor antigen release from cancer cells. Antigens are captured by dendritic cells, triggering a greater presentation at the lymph nodes. This would increase T cell circulation and recruitment at the tumor site, leading to priming and activation of effector T cells. Activated effector T cells flow into the systemic circulation and are trafficked to the cancer microenvironment through adhesion to tumor endothelium. Recruited from the circulation, they infiltrate the tumor, where they precisely detect and destroy tumor cells. Interestingly, tumor cell killing helps liberate more antigens, resulting in cycle prolongation.

In the last 30 years, several preclinical cancer models showed immunological changes in the tumor microenvironment following FUS. It has been hypothesized that FUS anticancer immunity interplays at numerous points by boosting tumor antigen release through the disruption of cell membranes. FUS can also promote dendritic cell maturation through improved expression of damage-associated molecular patterns (DAMPs). By mechanically disrupting the stroma, FUS leads to better antigen flow to lymph nodes. This leads to enhanced permeability at the tumor microenvironment and increased endothelial adhesion, molecule expression, and possibly proliferation of intratumoral T cells.

The FUS scientific community has gathered in workshops to share and merge novel findings. Assumptions have been made about changes that occur in the tumor microenvironment after ablative FUS causes the tumor to be more permissive to T-cell infiltration and immune attack. The early cytokine response induced by FUS needs to be studied. These immune responses may be short-lived and dependent on tumor type, treatment modality, type of

cell death, and cell types that persist after treatment. Cytokine profiling and biomarker identification are urgently needed to enable the monitoring of therapy. The diverse FUS conditions applied in different tumor types makes it challenging to recognize appropriate FUS parameters that may achieve the desired antitumor response. Sonication patterns, instrumentation, and strategies should be detailed and made readily available to the community.

Interesting observations were noted in preclinical studies. Distinct tumors can be different in the ways they react to the same treatment. Mapping local and distal transcriptome effects post-FUS can offer insights on how tumors respond acutely and durably with respect to the treatment. Combined treatment of checkpoint inhibitors and FUS can activate immune response and target tumor cell death.

1 Question to Dr. Ferrara

What are the immune effects induced by FUS in your findings?

The combination of thermal ablation and CpG vs. thermal ablation and anti-CD4 were studied to analyze their systemic impact. Interestingly, a distal immune response was seen when the immune system is stimulated by heat-fixation protocol. The impact of such a combination was noted across different types of cancer.

Second, prostate adenocarcinoma and HER2 positive breast carcinoma mouse models were compared to a pancreatic cancer model. Post-treatment results elicit different antitumor and inflammatory immune responses within the tumor microenvironment between cancer types. Cytokine release could be highly inflammatory in very dense tumor cells.

2 Question to Dr. Allen

What does the need to include DAMPs or anti-CD40 infer with respect to the type or intensity of damage induced by ablation? Why is “priming” or conditioning the tumor microenvironment (TME) important?

DAMPs are expected to demonstrate cell death. However, the nature of cell death describes DAMP release. Apoptosis, necroptosis, pyroptosis, or ferroptosis lead to the release of diverse forms of DAMPs. Developing strategies to regulate cell death pathways is critical at this level. Cell death patterns can be affected by the type of drug given prior to ablation.

3 Question to Dr. Frank

Do different tumor models or different tumor types substantially differ in the response of their immune components to ablative FUS?

We still cannot answer this. Our work with mechanical ablation involves significantly lower peak pressure and time-averaged power compared with thermal ablation. Given this fact, this approach shows different effects among various tumors. However, the overall immune response is transient due to the fast weakening and lack of ultrasound waves that spread to the whole tumor.



Left to right

Awdre Gamache, PhD

Tao Sun, PhD

Joseph Frank, MD

4 Question to Dr. Khokhlova

How do we control the types of immune cells that FUS traffics to the tumor? Recognizing that FUS can sometimes lead to immunosuppression because the “wrong” cells are trafficked. How does this play into the importance of timing of FUS with respect to other drugs, drug combinations, etc.?

Our work is centered on boiling histotripsy. This technique induces a strong and consistent immune response that causes the recruitment of dendritic cells and CD8 T cells immediately to the tumor microenvironment. Reported cytokines are similar to those released in other types of histotripsy.

5 Question to all

Are there any transcriptomic data similarities between histotripsy approaches and thermal ablation?

Dr. Khokhlova: We are doing a comparative study in pancreatic cancer to look at the dynamics of the immune response to histotripsy, boiling histotripsy, and thermal ablation.

Dr. Allen: Histotripsy induces the release of DAMPs, including the nonhistone nuclear binding protein (HMGB1). Elevated levels of HMGB1 have been observed within the tumor and serum after treatment. HMGB1 can stimulate a strong immune response that drives inflammation and tumor cell death.

6 Question to Dr. Gamache

How would spatial assessment and profiling of the tumor be useful?

Spatial profiling aims at allocating multiple cell types to their location and/or histological sections. Spatial omics technologies allow the spatial differentiation of the tumor microenvironment by developing exact spatial coordinates of cellular and molecular profiles. Such a tool can expand drastically the application of FUS therapy in cancer.

7 Question to Dr. Sun

Do different tumor models or different tumor types substantially differ in the response of their immune components to ablative FUS?

A preclinical study of GBM in an invasive mouse model has shown changes in the immune response after delivery of FUS combined with an anti-PD1 agent. Anti-PD1 expression was elevated post-treatment. The selected GL261 mouse model shows highly invasive and necrotic features yet is broadly vascularized. Alterations in the immune response may be detected between animal models. The subsequent step is to determine how to sustain such responses. Additional preclinical work is needed at different time points.

8 Question to Dr. Frank

Is there any development in the downstream analysis of liquid biopsy assays using machine learning or complex regression algorithms to help detection of biomarkers?

We need to a rigorous study of endothelial cell dynamics and their interaction with tumor cells. The endothelium in gliomas is highly permeable and leaky. Discerning the quality, leakage, and programming of tumor endothelial cells can directly support detection of biomarkers.

9 Question to Dr. Ferrara

What are the unique qualities of the immune response to ablative FUS compared with other energy-based treatments?

FUS is an adaptable approach that enables delivery of immunomodulatory agents to the brain. There is a need to study what happens within the tumor microenvironment. There is a diversity of immune cells related to each cancer type; controlling the cancer milieu is essential to modulate it.

10 Question to all

According to your experience, how should FUS-enhanced liquid biopsy be integrated as a therapeutic modality into the routine care of patients at advanced disease stages?

Panelists agreed on the importance of discerning the nature of immune response mechanisms induced by FUS. Panelists pointed out the need to compare successful and unsuccessful FUS experiences to better recognize biomarkers of therapeutic efficacy.

• • • • •

Cancer Immunotherapy— *Looking to the future*

MODERATOR

Jill O'Donnell-Tormey, Cancer Research Institute

PANELISTS

John de Groot, UCSF Medical Center

Patrick Dillon, University of Virginia

Alayna Hay, Virginia Tech Animal Cancer Care and Research Center

Natasha Sheybani, University of Virginia

Yingxiao Wang, UC San Diego



Jill O'Donnell-Tormey, PhD

Chief Executive Officer and
Director of Scientific Affairs
Cancer Research Institute



View on the Foundation's
[YouTube channel](#) >

Dr. O'Donnell-Tormey discussed the progress in the stimulation and modulation of the immune system in treating cancers. The immune system can lead to long-term and lasting responses in many cancers. Tumor immunotherapy has considerably improved disease management, with the FDA approving various agents across different cancer types. Yet the advancement is still considered slow, with minor subclasses of patients achieving a complete response. The field should be studying the emerging applications of FUS modalities in combination with immune checkpoint inhibitors (ICIs).

Dr. O'Donnell-Tormey advocated the reverse translation approach. Through this methodology, researchers collect real-time human clinical data, then take it back to the lab to look at the mechanisms and get insight into new combination therapies. Analyzing differences in treatment response can give a deeper understanding of the biology in nonresponders.

Dr. Dillon discussed combination therapies in clinical trials. The first trial evaluates the use of HIFU in combination with pembrolizumab in metastatic breast cancer patients. Clinical outcomes show differences between responders and nonresponders in terms of biomarkers and transcriptomics. The second trial assesses the combination of ablative FUS with low-dose gemcitabine in patients with early-stage breast cancers. The outcomes include the effects of immune response in these three treatment groups.

Dr. Hay explained her laboratory research work treating the canine model of spontaneous-occurring osteosarcoma. This animal model serves as a valuable translational prototype for the study of human bone tumors. This study assesses the safety and feasibility of using histotripsy in treating osteosarcoma in dogs. Insights into the complex response of the tumor microenvironment to the treatment are explored.

Dr. de Groot evaluated multiple FUS approaches for the management of brain tumors and metastases. Low response rates, toxicities, and resistance to immunotherapy remain a challenge in brain cancer treatment. Preclinical work with ICIs for GBM resulted

in a better survival rate. Yet, in one clinical application, there were no improvements in progression-free survival (PFS) or overall survival outcomes with newly diagnosed or recurrent GBM patients. FUS may be a potential combinatory partner with immunotherapies. Minimally invasive FUS-induced BBB opening can prompt an immune response and lead, for example, to the release of ctDNA. This novel approach promises discoveries about correlative biology and will ultimately guide better treatments. Ongoing clinical studies test combination treatment of ICIs in a neoadjuvant approach.

Dr. Wang is specialized in engineering controllable chimeric antigen receptor (CAR)-T cells via synthetic biology and ultrasound. Such development of inducible CAR-T cells can prevent on-target off-tumor toxicity and lead to the success of malignancy treatment. Another approach in the making is the development of engineered nanoparticles for cancer vaccination. Such a strategy can modulate tumor cells to produce clinically validated antigens serving as targets for CAR-T cells.

Dr. Sheybani emphasized bringing FUS into the era of precision oncology. She briefly described the major strengths of FUS as a non-invasive and non-ionized technology. However, technical improvements are essential to expand the therapeutic window for FUS therapy and to enhance treatment monitoring.

1 Questions to all

What clinical disease targets are ideal for FUS plus immunotherapy combinations?

Dr. Dillon: I think we should build on the fact that we can use FUS in most parts of the human body aside from the lungs. FUS even showed potential to access deep tumor tissues. Renal, prostate, brain, breast, and skin cancers make possible targets for FUS. Questions should be centered on the unmet needs in terms of an immunological standpoint. Lack of biomarkers for immunotherapy needs to be addressed. In breast cancer, there is huge unmet need in immunotherapy. Therapeutic FUS should be perceived as an option across the multitude of solid tumors.

Dr. de Groot: It is important to identify key features and appropriate study designs for FUS clinical trials.

Dr. Wang: It would be interesting to systematically collect tumor tissue samples post-FUS treatment in different modalities across various tumor types. This allows transcriptome tracking and ultimately can help engineering more specific targeting cells.

Can repeated biopsy be considered in clinical trials of FUS combination therapies?

Dr. Dillon: It depends on the site of the tumor. Repeated biopsy feasibility is dictated by the ethical use of multiple biopsies as well as the patient's tolerance. It would definitely offer means for continuous disease monitoring and ample immunohistochemical analysis and changes over time. Nevertheless, repeated biopsy may negatively affect the outcome of patients, or may be associated with an increased risk of perioperative complications.

Left to right

Natasha Sheybani, PhD

Yingxiao Wang, PhD



2 Question to Dr. Sheybani

Are we in a stage where we know enough about the effects of FUS that we can select appropriate drugs?

Or are we still doing trial and error?

Or just using the standard CTLA-4 and PD-1, PDL-1?

Looking at the literature, the attention is more centered on the selection of established drugs like ICIs. This holds an opportunity to learn about the effects of FUS and reinforce its role through the massively gathered data. Nonetheless, investigational novel immunotherapy, sonogenetic CAR-T cells and vaccination approaches are certainly prospective options for combination with FUS. Systematic efforts need to be deployed to properly select future investigational clinical trials.

3 Question to Dr. Hay

Do you consider multiple biopsies in the canine model of spontaneous occurring osteosarcoma?

We cannot perform serial biopsies due to the risk of pathological fractures. Surgical resection is performed one day, 3 days, or 5 days after histotripsy treatment. FUS has a promising role in providing pain palliation associated with osteosarcoma.

4 Question to all

What metrics other than T-cell ratios can be used to predict clinical success?

Dr. Wang: The integration of FUS and synthetic biology will present further opportunities to engineer macrophages for FUS activation. Ongoing and scheduled clinical trials comprising CAR-T cell therapy in malignant gliomas are paving the way for its use in clinical settings.

What about window-of-opportunity clinical trials with FUS? Can blood samples in the absence of biopsies reliably predict response?

Dr. de Groot: The upcoming clinical trial is evaluating the feasibility and efficacy of FUS with neoadjuvant PD-1 blockade in recurrent, resectable GBM. Treatment tissue sampling and blood sampling will be collected for measuring outcomes and response detection. One could discuss conducting comparable studies using CAR-T cells.

Dr. Dillon: The current ongoing clinical trial in early stages of breast cancer will assess the effect of FUS plus a chemotherapy drug. Yet, the importance of time to surgery remains a concern in early curative cancer stages. Thus, the timing of FUS can be really challenging in such settings. Quite the reverse, prostate cancer is a slow progressing tumor in early stages; therefore, the time for window of opportunity trials is long enough. Another prospect is bringing into the conversation opportunities for FUS with respect to targeting specific oncogenes and gene therapy. Such a modality can be considered as a golden opportunity to impact the tumor microenvironment. Incorporating functional imaging would as well heighten corresponding results.

Left to right

Yingxiao Wang, PhD

Alayna Hay, PhD



Dr. O'Donnell-Tormey: The high cost of ICIs or immunotherapy can delay clinical studies. This can be addressed through clinical trial grants and funding and clinical accelerator initiatives or programs. Alternatively, working in a clinical model where the drug is already approved could enable payment for the drug via insurance.

What are the realistic opportunities for FUS in the next decade, in terms of areas of clinical impact?

Dr. Hay: Researchers are investigating advancing FUS devices to perform a fully noninvasive ablation of tumors and augment immune response.

Dr. Wang: Advancements in-genetic sequencing techniques will allow favorable translational perspectives for the use of FUS stimulation in the diagnosis and management of cancer.

Dr. Sheybani: We need to mine deeper in immunology and functional imaging data via machine learning and other AI-driven approaches to reconcile FUS data and enable predictive modeling.

Dr. de Groot: Targeting tumor-associated macrophages with FUS brings exciting opportunities to the field of GBMs.

Dr. Dillon: The development of precision FUS and noninvasive gene therapy holds great promise toward advancing and improving the treatment of patients with cancer.

• • • • •

Machine Learning and FUS

MODERATOR

Rick Hamilton, Focused Ultrasound Foundation

PANELISTS

Bingbing Cheng, ShanghaiTech University

Matthew Howard, Amazon Web Services

Tianxi Li, University of Virginia

Charles Guttman, Brigham and Women's Hospital

Allison Payne, University of Utah



Rick Hamilton

*Managing Director,
Chief Technology Officer
Focused Ultrasound Foundation*



View on the Foundation's
[YouTube channel](#) >

Mr. Hamilton began by saying we know that machine learning (ML) is being used in health care, e.g., in radiology to improve diagnosis, and radiation therapy to improve efficiency and quality of care, but we do not know how, why, and where ML will have the greatest impact in focused ultrasound. We will not move forward with platitudes and high-level generalities, but neither should we do not want to dive into the weeds. We need to find the middle ground—not ML for the sake of ML. We need to identify high-value use-cases, with incredible impact. We need to understand at a high level how to apply these tools, and we can learn from others' successes and failures.

Dr. Cheng started a lab that explores technology for brain applications—acoustic cavitation, AI—and translational research in those areas.

Dr. Howard is head of data science for Amazon Web Services Healthcare, part of an international team to transform health care using cloud technology data science and machine learning to improve health outcomes.

Dr. Li researches modeling and ML to understand connections in complex systems, e.g., social networks, traffic, or international systems. Specifically, he studies modeling brain activity with brain MRI or by making imprints of gene coefficient networks.

Dr. Guttman works on bridging the medical and the engineering communities. He applies imaging techniques to neurological diseases, like multiple sclerosis, to quantify disease volumes, clinical outcome structures, and functional outcomes. He is developing an informatics system for a virtual laboratory that allows data-sharing as well as applications.

Dr. Payne focuses on MRgFUS in breast cancer, and tools to modify and assess therapy. Developing new imaging biomarkers will also be useful. More and more data are available, and ML is a way to leverage that data, whether our interest is in prediction or correlation with histology or ischemic heart disease.

1 Questions to all

What use-cases and technical approaches hold the most promise for ML in FUS?

Mr. Hamilton: The hard part of doing ML is asking the right questions to get the right data, e.g., predicting patient movement during ML, which will influence ML outcomes.

Dr. Payne: We have large datasets at our disposal. If aptly curated, they would be very useful, e.g., responders vs. nonresponders, or BBB assessment using acoustic data.

Dr. Cheng: An important issue is how to quickly and accurately assess the BBB opening or to know whether it is in fact open. Currently, we use contrast-enhanced MRI, but that requires an injection of contrast material and access to an MRI scanner, so it is not used for every patient. They just assume the BBB is open, but the character of openness differs among patients. We also have acoustic data using microbubbles, which offers an opportunity to predict or review the BBB opening.

Dr. Guttman: We have mostly studied essential tremor, for which he finds ML to have an application in the planning phase and the prognostic post-op phase. ML is correlated to accurate prediction of pressure, target recognition, etc. It could be applied to anatomy, as in finding the relationship of images to the organ. Generating synthetic imaging contrasts has been successful, including in thalamic anatomy for which some contrasts are not routinely acquired. ML allows better direction to targets and substrates. More complex in the planning phase is dynamically adapting planning over time to account for anatomic changes over time. ML on large datasets is undertaken to understand when tremor or other side effects will recur.

Which ML tooling approaches do we need to be aware of and which have the greatest potential value?

Dr. Li: Frameworks can be used to solve many problems. Ultrasound imaging data can be useful, but details of the needed machinery have not been worked out. High-level perspectives must be open to different types of learning. Clinical trials often yield small sample sizes, but, even so, we can measure different cell components of gene expressions. Studying complicated new networks may not give better results. The advantage of ML could be in interpretation. Using simple measures tends to get better interpretations. So, using very basic techniques may be better.

What are the biggest challenges to overcome in applying ML to drive meaningful FUS results?

Dr. Howard: We have been regulating software for years. A lot of medical device regulations (MDRs) contain increasingly useful guidance. The information is out there but may not be in the right places. A regulatory framework (the source of truth) starts with a device regulator. It is useful to be told how to do things. To get to the right source of information, start with the MDR. A general observation on use-cases is that they are very complex and specific. But wrapped around them are other, often very boring, issues that would be of high value if automated. Automation would make them easier to use. Start with something that has research applications, so you are not

Left to right

Rick Hamilton

Allison Payne, PhD



immediately subjecting a patient to newly developed processes. First develop the ML; then, if applicable, try it with patients.

Dr. Guttman: I disagree. Having clinical datasets on tremor, for example, does not imply jumping into clinical research, nor does it mean that you will immediately apply it to patients.

What can we learn from other health care ML successes?

Dr. Guttman: Data collection offers an opportunity, although it will not immediately get to clinical use. Secondly, collaboration will be essential. Much data is already collected and quantified, and it would be a useful playing field for AI scientists.

Dr. Payne: Standardization of medical collection. At a presubmission meeting with a regulatory agency, they tell you the exact endpoints they want to see, which has driven clinical research.

Dr. Howard: In addition to the research and modeling pieces, we should think about clinical workflow and how these technologies fit together. The model may be great, but if it does not work easily in a clinical setting, it will not be used. That depends on how it fits in and how to manage it. We must also keep focused on the endpoint and prevent “model drift.” We build models to address new challenges, but we must also know how they fit into daily practice.

5 What advice or guidance would you offer for those seeking to apply ML in FUS therapies?

Dr. Payne: At her lab, they let their students lead. The students came up with questions and how to investigate for answers to them, and by doing that, they discovered other interesting questions.

Dr. Cheng: Talk to people who do not have the same background you do, but whose information you need.

Mr. Hamilton: FUSF will help by aggregating resources.

6 In BBB work, instead of using contrast medium to see that the BBB opening had been achieved, would it be possible to estimate when it was closed?

Dr. Cheng: I collect information during treatment and do not use a general calculation. I just convert data in that domain and do not select values. I gather data and use it in prediction models. For damage prediction, I can get good results, but for opening the BBB, we can achieve only a 60% success rate. We have not yet considered closure.

7 About the use-case of the BBB opening: Given the variety of outcomes, what can ML offer over conventional signals and outcomes?

Dr. Cheng: The benefits of ML are for the area under the curve. With ML you can extract much more data for accurate prediction, although different groups have different outcomes. Currently, there is no universal standard for ML, but he hopes to find one.

• • • • •

Brain Imaging Guidance, Targeting, and Monitoring

MODERATOR

Jean-François Aubry, Physics for Medicine Paris

Suzanne LeBlang, Focused Ultrasound Foundation

PANELISTS

Vibhor Krishna, University of North Carolina at Chapel Hill

Hao-Li Liu, National Taiwan University

Nathan McDannold, Brigham and Women's Hospital

Lennart Verhagen, Donders Institute for Brain, Cognition and Behaviour, Radboud University



Jean-François Aubry, PhD

CNRS Research Director
Physics for Medicine Paris



Suzanne LeBlang, MD

Director of Clinical Relationships
Focused Ultrasound Foundation



View on the Foundation's
[YouTube channel](#) >

Dr. Aubry listed key unanswered questions to guidance, targeting, and monitoring of FUS. There are limitations of current treatment planning models, and they need to be revised to account for thermal treatments and tissue changes. Another question that needs to be addressed is how to confirm target engagement and safety with neuromodulation—some options may include MR-ARFI, fMRI, and functional ultrasound imaging. There is a safety consortium, International Expert Group on Transcranial Ultrasonic Stimulation Safety and Standards (ITRUSST), that will be publishing an expert consensus on safe neuromodulation parameters.

Dr. LeBlang reviewed the different methods for controlling BBB opening but noted that precise control over the level of BBB opening and correlation with the resulting MRI enhanced region has not been achieved. Confirming and monitoring treatment is a key area of interest in the field and to regulatory bodies.

Dr. Krishna explained that his research focuses on ET and PD and that one of the biggest challenges is accurate and precise planning for thermal ablation treatments. Thermography also shifts in localization during the procedure. Multimodality methods may help to overcome these challenges. Understanding lesion characteristics that lead to long-term success using imaging methods like diffusion MRI is another area of active research.

Dr. Liu talked about neuronavigation for the guidance of FUS. He hopes to respond to those that claim that neuronavigation isn't a viable option for performing FUS procedures in the brain because it lacks guidance and monitoring.

Dr. Verhagen explained his interest in integrative neuroscience. It is important to keep in mind that for neuromodulation, planning and targeting must be calculated in three dimensions, not only in the anatomical space but also in intensity. Neuromodulation is also dependent on neuroactivity, neurophysiology, and neuroanatomy.

Dr. McDannold's early work used MRI-based methods for thermal monitoring of FUS therapy. As his team became more interested in microbubbles for delivering treatment, the focus shifted to using acoustic measures to monitor and control microbubble-based FUS treatments. The team also works with preclinical models and clinical trials.

1 Question to all

What are the limitations of current treatment planning models and are they sufficiently accurate for transcranial applications?

Dr. Aubry: Aberration correction during the planning process is important. There are models for treatment planning, but accuracy remains an unanswered question. Validation must also take place in a variety of human skulls because of the wide range of variability between patients. Machine learning could be helpful with analyzing a wide range of variability.

Dr. McDannold: My team is using machine learning to analyze data from ET FUS treatments. They've found that data can vary by orders of magnitude between patients.

Dr. Liu: The computational effort is a topic for further discussion. The real-time calculations for treatment planning take quite a bit of time, and machine learning could decrease the time needed to calculate pressure.

2 Question to Dr. Krishna

Can you elaborate on the effect of increasing power and the variability in target coverage of what is observed versus what was planned?

Smearing of the focus is often observed in unexpected directions as power is increased. The planned volume of treatment and the actual treatment volume are often different. The challenge is to ensure there are no off-target locations. Having an available method to model and anticipate these off-target effects would greatly improve patient safety. Repeatability of targeting in three dimensions is also needed to advance the field. Skull heating also shifts the focal spot in different directions and anticipating and compensating for this change is an important consideration.

3 Question to Dr. Aubry

Please explain how neuromodulation could be used for treatment planning of thermal exposures.

This is constantly changing with additional research. Even a year or two ago, he believed that a thermal rise would be necessary to confirm target location. But neuromodulation can achieve strong target engagement and patient engagement at low power; one example is ET. Neuromodulation could be used to check targeting, but this might be difficult for neurosurgeons to accept.



Left to right

Suzanne LeBlanc, MD

Jean-François Aubry, PhD

4 Question to Dr. Aubry

Accurate modeling is based on acoustic parameters calculated from CT data, but the acoustic parameters differ widely between groups. Is there a way to reduce this variability?

Dr. Aubry: Comparisons of the available models use similar parameters on a single skull. The next step is to compare the models using a wide range of skulls and the parameters that are used (max and min speed of sound, bone density, etc.). These are rough models that allow adjustment for an individual patient. At some point, a standardized model should be used across all institutions.

Dr. McDannold: They are currently using simulations to compare the temperature rise to predict the heating that occurs during FUS thermal ablation for ET. They are expanding this to match not only a point in space, but also the shape of tissue heating. Another area that needs further investigation is why peak temperature is harder to achieve the longer that thermal ablation is applied. What parameter in the skull model leads to the change in target heating?

5 Question to Dr. Verhagen

What is the best method for readouts of target engagement for neuromodulation?

Target verification and target engagement are separate issues. Target verification is a direct effect of physics on the physiology. There is no good method to ensure target engagement. Target engagement is a direct effect of physics and physiology. Target engagement will be the ability to see neurological changes in the brain due to a treatment and is more challenging. For ET, there is a clear effect of target engagement. For other disease states, the effects are more subtle and not immediate. We need to establish new methods to determine target engagement, and imaging could help.

6 Question to all

How can animal models help with target engagement for neuromodulation?

Dr. Verhagen: Both human and animal models should be investigated in parallel. For clinical populations, it would be helpful to know whether the target is an excitatory or inhibitory circuit, and this information is unavailable at this time. Research in animal models could help understand target engagement.

7 Questions to all

Is there a benefit to adopting clinical technology into preclinical research?

How to adapt the technology to help with clinical translation?

Dr. McDannold: BBB opening is dependent on ultrasound frequency, and the same frequencies cannot be used in mice. It is also difficult to find disease models in larger animals, so it is difficult to perform preclinical research.

What can be done to improve monitoring for BBB opening?

Dr. Liu: Neuronavigation guidance lacks feedback but could be used for BBB opening. Acoustic feedback could be used to compensate. A phased array transducer can perform phase correction and also provide imaging in place of focal beam mapping.

Dr. McDannold: Preclinical work was not predictive of clinical patients with GBM. The infiltration of GBM was mostly in white matter, which is not the case in humans. High bubble doses were also given to animals, but this dose cannot be given to humans. The human skull is much thicker than in preclinical models and has to be accounted for in modeling. Pretreatment imaging prior to microbubble injections could be used to understand thresholds. We are currently trying to analyze differences in gray and white matter during BBB opening.

Could Acoustic Radiation Force Imaging (ARFI) be used for BBB opening?

Dr. McDannold: ARFI is most likely of potential use for neuromodulation because of a lack of feedback and thermometry. If the exposure levels of ARFI are higher for neuromodulation, that would be a barrier. Probably less important for BBB opening since there are other methods for verification.

Dr. Aubry: In principle it should be possible to use ARFI at low intensities, but it lacks sensitivity. The energy required for neuromodulation with ARFI was much higher than with FUS. If the sensitivity could be increased, it might be possible.

What is the greatest unmet need?

Dr. Verhagen: MR-ARFI has a lot of potential. Improving the physical verification of targets both with ultrasound imaging and MRI could move the field forward.

Dr. Liu: Hopeful that ultrasound imaging can play a greater role in targeting.

Dr. McDannold: Skull variation is a large challenge for thermal ablation. Having access to 3-dimensional temperature mapping would help avoid side effects. For BBB opening, having a better understanding of the bubble population and using this to improve treatment planning is also greatly needed.

Dr. Aubry: The needs for imaging, guidance, and monitoring are different for each application of FUS, including histotripsy, BBB opening, thermal lesioning, and neuromodulation. There may be potential to apply solutions from each of these to the other applications.

Dr. Krishna: Clinicians need to consider both efficacy and safety, and the ability to make better decisions on planning for safety is very important.

• • • • •

Attending virtually, left to right

Lennart Verhagen, PhD
Vibhor Krishna, MD

Seated, left to right

Suzanne LeBlang, MD
Jean-François Aubry, PhD
Nathan McDannold, PhD
Hao-Li Liu, PhD



Gynecologic Indications

MODERATOR

Martijn Boomsma, Isala Hospital

PANELISTS

Kullervo Hynynen, Sunnybrook Research Institute, University of Toronto

Bilgin Keserci, Universiti Sains Malaysia

Suzanne LeBlang, Focused Ultrasound Foundation

Johan van den Brink, Philips



Martijn Boomsma, MD, PhD

Radiologist
Isala Hospital



View on the Foundation's
[YouTube channel](#) >

Dr. Boomsma presented the latest findings and lessons learned to date from the use of MRgHIFU in uterine fibroids. Nowadays, literature reviews recommend complete ablation of the growth rather than applying restrictive treatment protocols in uterine fibroids. Systematic reviews show that HIFU treatment is associated with a 0%–21% re-intervention rate 3–34 months after the procedure. The symptom severity score decreased by 60% over 12 months and quality of life increased by 31% during the 6-month follow-up period.

In the FUS myoma outcome study (FUMOS), the re-intervention rate was assessed as long-term outcomes after MRgHIFU therapy. Unrestrictive MRgHIFU treatments led to reasonable re-intervention rates of 18% at 40 months follow-up. It also seems that HIFU treatment can reduce the treatment-to-pregnancy interval post-HIFU intervention.

Overcoming challenges detected with MRgHIFU therapy is essential to increasing eligibility for treatment. The development and clinical evaluation of a 3-step modified manipulation protocol for MRgHIFU of uterine fibroids helped refine eligibility to treatment and increased therapy effectiveness. Therapeutic success of MRgHIFU is frequently measured by the percentage of nonperfused volume (NPV) compared with the total volume of the fibroid pretreatment. A high NPV of 63% is related to clinical effectiveness.

Moreover, the application of a multiparametric MRI for uterine fibroid tissue characterization and treatment monitoring may be a valuable tool to predict treatment outcome and determine the optimal treatment modality.

The T2 corrected intravoxel incoherent motion (IVIM)-based model was noted to better characterize uterine fibroid tissue. The latest reports document improvement following MRgHIFU therapy for uterine fibroids using the IVIM-based model.

Erber et al. showed that the short-term outcome for the treatment of symptomatic fibroids in a myomatous uterus by MRgHIFU is clinically similar to that of solitary fibroids. Li et al. explored the value of whole-tumor region of interest ROI (ROIwt) analysis for quantitative perfusion in predicting immediate ablation response of uterine fibroids in

MRgHIFU. The ROIwt quantitative perfusion parameter could be a possible predictor for the immediate ablation response.

However, despite favorable clinical outcomes, application of MRgHIFU in routine practice is still challenging. Cost-effectiveness health technology assessments should be carried out. The effect of direct versus indirect ablation on NPV ratio should be evaluated. Lack of robust evidence hinders the proper adoption of MRgHIFU in the fibroid care plan. Prospective mid- and long-term clinical effectiveness evaluation through randomized controlled trials will facilitate the inclusion of MRgHIFU in uterine fibroid care guidelines.

In this context, a new randomized controlled trial, the MyChoice Study, will evaluate the long-term cost-effectiveness of MRgHIFU compared with invasive and minimally invasive uterine fibroid care, such as hysterectomy, myomectomy, and uterine artery embolization. The primary outcomes of the study are quality of life at 24 months post-treatment and cost of treatment.

Dr. Hynynen reviewed the history of MRgHIFU devices. The first and still-used Chongqing Haifu-US imaging-guided device effectively treated more than 200,000 patients in 28 countries. Yet, it does not offer real-time guidance.

A novel MRgFUS thermal ablation system developed by Insightec for uterine fibroids offers patient-specific treatment planning. Parameters can be adjusted to ensure that optimal response and treatment is guided in real time by MRI. A similar device was also created by Philips and marketed by Profound, a corporate business intelligence service.

Similarly, another modern Chongqing Haifu device has a single transducer integrated into the patient table and fronted acoustic lenses that permit focus-length adjustment. Additionally, another ultrasound-imaging device is equipped for real-time monitoring. However, these devices are limited in the control of focused electronics. Researchers are working toward establishing fully electronically steered phased arrays of 6,144 elements independently driven and controlled by electronics. At present, a phase I clinical study is assessing the vast potential of this technology to perform safe, precise, and rapid ablations of large volumes.

Dr. van den Brink explained Philips's approach in expanding the impact of MR from diagnosis to treatment. This is achieved by growing an accurate and personalized MR-guided therapy with integrated workflow and adaptive treatment for every patient. Researchers are also engaged in integrating the use of companion diagnostics and tumor control in emerging multimodal treatments.

The application of AI-enhanced reconstruction methods will allow for significantly faster scanning. The primary aim is to have one common real-time connect architecture or interface that serves multimodal cancer treatment. Also, implementation of MR-only planning and monitoring could enhance the spatial accuracy of radiotherapy. MR delivers unique quantitative and metabolic biomarkers such as amide proton transfer-weighted (APT_w). This potential biomarker is being explored for assessing chemotherapy response in breast cancer patients.

Dr. Keserci evaluated the role of AI in predicting the treatment outcomes of HIFU ablation of uterine fibroids. Investigations are centered on developing classical and quantum AI analysis for fibroid classification. The use of a whole-tumor analysis was shown to be more appropriate. Through a retrospective multivariate analysis, Dr. Keserci studied the impact of a multiparametric MRI-based machine learning model in predicting clinical success preoperatively for HIFU ablation of uterine leiomyomas. Achieving an NPV ratio of $\geq 90\%$ as a measure of clinical treatment success shows promise in the clinic and is safe. Effective machine learning techniques, features, and algorithms are essential to achieve treatment outcomes.

Dr. LeBlang highlighted the insurance barriers for MRgHIFU therapy of uterine fibroids. No major insurance company offers reliable coverage and reimbursement for FUS treatment of fibroids. Techniques that expand patient selection and deliver safe, rapid, and efficient processes should be devised.

1 Question Dr. van den Brink

Do new MRI hardware and software interface developments affect cost of patient treatment?

First, we need to leverage economies of scale. MRI systems employed for therapeutic interventions should be billed based on the same platform of that used for diagnostic purposes. Second, we need to leverage programs for interface reconstruction and innovative integrated software that function in multiple scenarios. Developing compatibility between advanced MR systems and best-quality integrated software will expand access to MRgHIFU treatment and lower the cost of care.

2 Questions to Dr. Hynynen

Do the new MRI hardware and software developments affect treatment time?

Based on the calculated physics, I expect a decrease in MRgHIFU treatment time by at least 50%.

How can we target nonhomogeneous areas of tissue and how close to the skin can we generate energy beam?

I think with proper manipulation techniques, we can tackle such concerns. Also, running the device at a high energy level would generate adequate waves and overcome such issues.

3 Questions to Dr. Keserci

How well can we estimate the 63% of nonperfused volume?

We are examining higher NPV percentages. A high NPV percentage is closely related to clinical effectiveness. Our retrospective study intended to examine MRI features influencing an NPV ratio greater than or equal to 90% post- HIFU treatment without sacrificing patients' safety. Such evidence can convince practitioners to adopt an HIFU system. Machine learning is very promising in feature selection and prediction of outcomes, yet it is mandatory to gather new and validated data to build reconstruction algorithms.

Attending virtually, left to right

Kullervo Hynynen, MSc, PhD
Bilgin Keserci, PhD

Seated, left to right

Martijn Boomsma, MD, PhD
Suzanne LeBlang, MD
Johan van den Brink



How to predict appropriate ablation time and the level of energy deposition?

It is dictated by fibroid tissue characterization, as well as fibroid volume size and number and technical limitations.

4 Question to Dr. Hynynen

How will the new MRI hardware positively influence the amount of energy that can quickly deposit in tissues?

The latest developments in MRgHIFU techniques provide full programmed control of the HIFU energy deposition. High-power ultrasound beams can be focused rapidly into target areas.

5 Question to Dr. LeBlang

What are the future perspectives for MRgHIFU treatment for uterine fibroids?

Randomized controlled trials comparing long-term cost-effectiveness of MRgHIFU with standard fibroid care are critical to complete clinical adoption and reimbursement. Patient selection, technical sonication tools, and machine learning algorithms should be better developed.

• • • •

Technology Breakthroughs

MODERATOR

Kim Butts Pauly, Stanford University

PANELISTS

Hong Chen, Washington University in St. Louis

Rafi de Picciotto, Insightec

Ryan Jones, Sunnybrook Research Institute

Tatiana Khokhlova, University of Washington

Cyril Lafon, LabTAU INSERM U1032

Eli Vlaisavljevich, Virginia Tech

Zhen Xu, University of Michigan



Kim Butts Pauly, PhD

*Professor of Radiology
(Radiological Sciences Lab) and,
by courtesy, of Electrical Engineering
Stanford University*



View on the Foundation's
[YouTube channel](#) >

Dr. Lafon highlighted the work of the Georgia Institute of Technology group on a new technology of ultrasonic transducers: the capacitive micromachined ultrasonic transducers (CMUT) for opening the BBB, but also for listening to cavitation. The new approach gives flexibility to the probe since the transducer has a broader bandwidth for both imaging and therapy. CMUT technology brings obvious advantages but has faced robustness issues historically. New-generation transducers enable high output pressures to open the BBB and can also operate for a longer time to ablate tissue.

Dr. Chen highlighted the device developed by Jinhyoung Park and his team in the field of neuromodulation technologies. The equipment is based on a piezoelectric polymer polyvinylidene fluoride (PVDF) membrane placed directly on glass cover slides, on which cell culture experiments are then performed. This allows performing ultrasound sonication simultaneously with optical imaging by coupling the transducer directly to the cover slide. Additionally, absorbers directly capped to the objective minimize the issue of standing waves.

Dr. Khokhlova presented the work of Hong Chen's group on intranasal delivery of drugs to the glymphatic system. Through this technology, the drug propagates along the perivascular space rather than inside the vessels, through cavitation inside the vessels, which acts like a pump. Next steps would be to understand whether there would be applications in other parts of the body aside from the brain to transport molecules in the perivascular space as opposed to intravascularly.

Dr. Vlaisavljevich presented novel work in the field of ultrasound histotripsy, which has multiple interesting features, as it is noninvasive, nonthermal, and provides real-time data on treatment targeting as well as tissue feedback. When targeting the brain with histotripsy,

he highlighted work from the Michigan University group using magnetic resonance MR-guided systems as well as novel neuronavigation devices, which show acoustic cavitation feedback in which the real-time nature of ultrasound imaging of the bubble cloud that is observed in the liver is achieved in the brain.

Dr. Vlasisavljevich also highlighted recently published work from Francesco Prada on an intracranial ultrasound-guided implant for performing real-time procedures in the brain. He also described the work of Jeremy Brown in developing miniature handheld histotripsy systems, with high frequency for high-precision intraoperative ablation in the brain.

Dr. Butts Pauly highlighted the thermometry work of Steven Allen on the use of iron-based coupling media (IBCM) in transcranial procedures. The biggest benefit of the approach is allowing continuous circulation during the procedure, which minimizes skull heating but has to-date been impossible because using DI water as the coupling medium generates a large MRI motion artifact that obscures the brain anatomy (IVCM reduces signal from the water bath, thus reducing image ghosting).

Dr. Jones presented the work of Nathan McDannold's group in comparing acoustic emissions measured during brain treatments in GBM patients to radiographical findings. Results show that correlations within a patient are possible but are less obvious across the whole population, highlighting the need for refining the parameters to be studied. New devices allowing for increased cavitation-based control seem to increase the homogeneity of the cavitation delivered, leading to more efficient treatments.

Dr. de Picciotto discussed machine learning-related work from Shanghai Tech University and UT Southwestern Medical Center, whose groups use machine learning to predict BBB opening and tissue effect in a rat model; as well as work by Matteo Gionso measuring the distribution of microbubbles in a guinea pig perfused brain model. Along the same line, Dr. de Picciotto stressed the large number of parameters at play that makes it very challenging to look at correlations in the clinical setting. He challenged whether machine learning was the appropriate tool to predict BBB opening and whether a predictive tool was enough, or if BBB permeability or drug delivery needs to be confirmed when the patient is still on the table, taking into consideration that a single patient is not necessarily reflective of other patients and that parameters will always need readjusting.

Dr. Xu discussed the rapidly developing technology that couples neuronavigation-guided FUS with acoustic monitoring to perform brain treatment. This potentially allows treatment outside the MRI scanner while providing targeting/efficacy feedback. Issues remain with regard to BBB opening, microbubble distribution, and cavitation monitoring, but the new technology could eventually allow for bypassing MRI usage. Dr. Xu questioned which approach is best suited for solving such issues: acoustic monitoring, MRI, or a combination with machine learning, etc.?

Left to right

Ryan Jones, PhD

Hong Chen, PhD



Feedback from the audience and panelists on technological breakthroughs

CMUT is the most sensitive technology, as different layers in the brain have different vasculature, and CMUT allows capturing microbubbles at the different brain structures, especially the ones that have low vascularity (hence low microbubble concentration and low signal). The hardware of the CMUT allows for increased sensitivity.

With regard to controller aspect, especially for drug delivery, there is a need for fine-tuning the exposure conditions, especially in conditions of multiple administrations to prevent adverse effects.

Acoustic emissions data need to be monitored and recorded and will allow for understanding false positives or false negatives. Exablate treatments generate a large amount of data points that can be later fed to machine learning models depending on the questions. How machine learning will be used and what questions will be answered still need to be defined, probably from a clinical experience perspective. A very sensitive technology is needed for acoustic emission recording, and issues remain with regard to homogenizing the bubble administration method and quantity (across and within patients). A high number of variables are at play, starting with the tissue type (tumor, white matter, gray matter, etc.)

1 Question Dr. Ryan

Can ultrasound guidance replace MRI guidance for brain application?

In the context of BBB opening, where no strong information is derived from the MRI during the procedure, preoperative images for targeting and post-treatment images for evaluation could be deemed enough, whereas actual treatment could potentially be done outside of MRI. However, monitoring bubble emissions and mapping them spatially in the brain will be important, as well as capturing large amounts of data points. Issues remain with the different hardware, which are not able to capture all the acoustic emissions, potentially reducing the predictive capability of the bioeffects. The correlative significance between spatial bubble activity with the different bioeffect signatures still needs investigation.

2 Question to all

What features are missing in today's transducers?

Panelists agreed that a very wide bandwidth would be ideal and called for more affordable FUS systems that are more intuitive, easier to use, and more compact and portable. New-generation transducers would ideally be transmit–receive capable and would allow a wide range of pressures (from BBB opening to histotripsy).

.

Left to right

Rafi de Picciotto, PhD

Cyril Lafon, PhD

Eli Vlaisavljevich, PhD



Technology Gaps

How can technology breakthroughs lead to broader adoption?

MODERATOR

Elisa Konofagou, Columbia University

PANELISTS

Garry Choy, United Health Group

Pejman Ghanouni, Stanford University

Kullervo Hynynen, Sunnybrook Research Institute

Yoav Levy, Insightec

Andreas Melzer, University Leipzig

Brad Wood, National Institutes of Health

Graeme Woodworth, University of Maryland



Elisa Konofagou, PhD

Robert and Margaret Hariri Professor
of Biomedical Engineering and
Professor of Radiology (Physics),
Dept. of Biomedical Engineering
Columbia University



View on the Foundation's
[YouTube channel](#) >

In response to the opening question, the panelists identified gaps in the FUS field:

- Sonication of cell cultures for hyperthermia; for example, to sonicate the liver through the ribcage.
- The combination of radiation therapy and ultrasound is an underdeveloped area and has shown good results in research.
- Monitoring of ultrasound effects (such as temperature rise, edema, effusion) and its effect on killing cells.
- The need to bridge technologies to the clinic, such as bringing positron emission tomography (PET) MRgFUS to the clinic.
- The need to define the limits and gaps in technological approaches and their clinical applications.
- Increase in vivo readouts of FUS bioeffects, rather than using new contrasts on MRI to evaluate efficacy and imaging to evaluate toxicity.
- Be able to examine mechanical or thermodynamic effects resulting from FUS to better understand what happens from a therapeutic perspective and advance understanding in the field.
- Adoption of FUS in clinical use so that it becomes the treatment of choice.
- Shorter treatment times.

1 Question Dr. Ghanouni

If there were no limitations on resources, what would you want?

The limitations are broad. Physicians are constrained by software and planning devices. Many patients are excluded from treatment because of the software and technology constraints.

Physicians discuss the need to add therapy (such as adjuvant therapy) to ablation because ablation is not working. The goal must be to ensure that the primary therapy is working to avoid the need for additional therapies

2 Question to Dr. Woodworth

Please identify the current clinical advantages and limitations for ultrasound-guided and MRI-guided treatments, and how to improve those systems for faster adoption?

Many devices are available and in use, such as Insightec and NaviFUS, and new devices are coming to practice. These devices have different strengths and advantages. The challenge is to know which biological effect/impact we are going for and how to get a readout of the effect. Non-contrast on MRI is not enough; researchers must be able to compare the BBB opening, and how to compare the end effect across different tools. A readout can be the desired amount of immunomodulation. To advance research and application, there is a need to get better readouts about biological effects, especially in the brain. Researchers should be able to design tools and comparable downstream assays to enable us to compare Carthera BBB disruption to Insightec, to dynamic contrast imaging. New tools may be thought to have similar effect just because of contrast enhancement, and that is concerning and an important clinical gap

Researchers need to achieve BBB disruption and thermal ablation. Acoustic emission data and new changes on MRI are used to assess effects. There is a need for a deeper understanding of these effects outside the MRI world, and proper device comparison to make these technologies faster, efficient, and more reproducible in patients. This is a pivotal moment to get a better readout for faster adoption. New companies are coming in the space; it is important to be cautious and not to inflate expectations that may hurt patients.

Notably, the readout depends on ablation sites and can be more complicated in the brain. In some sites, MRI and ultrasound can give good readouts.

3 Question to all

Treatment time is the biggest gap. Can MRI-guided therapy become faster, or should ultrasound be used for guidance instead? Where can better treatments be found?

Dr. Hynnen: An important question is whether the permeability enhancement for the BBB opening can be made uniform. With ablation outside the brain, different devices need to get faster. The disadvantage with ultrasound guidance is that we cannot see the ultrasound propagation path like we can see in MRI.

Dr. Wood: Getting perspectives of a clinician and the physicists (underlying physical mechanism) is critical to understanding the benefits and advantages specific to HIFU. The benefit with therapeutic ultrasound is its weakness: clinicians do not understand the multifactorial space and bioeffects. This perspective will allow clinicians to tweak an intended bioeffect, a specific clinical need or unmet situation. For example, research by Dr. Hynynen has revealed mechanisms underlying effects, given certain parameters (mechanical, acoustics, etc.).

4 Question to Dr. Levy

If we had unlimited resources, what would be your priorities for the ideal FUS?

Early commercial systems have been used to treat essential tremor, yet the field is evolving. An important limitation is the treatment rate; hence the goal is to improve the commercial systems in a way that shortens treatment duration. Volumetric thermometry is an important building block of these systems. An accelerated volume thermometry has been developed in the current system that can give five slices of 2 mm in 3.5 seconds. However, we need to convince MRI vendors to integrate their (Insightec) system with the MRI. Additional features include the option to do echo-focusing, which is focusing based on measurements instead of predictions. In clinical trials, echo-focusing gave good results, though there is no use-case to include in our systems.

To improve drug delivery, the challenge in developing a product is to measure the resulting clinical outcomes. In addition, many unknown variables remain with regard to the efficacy of clinical treatments in drug delivery applications.

- 1 Which drug will benefit from these systems and will be able to cross the BBB and give good outcomes?
- 2 To what extent should outcomes be measured?

Other important questions include: How aggressive the opening should be, how many sessions does the patient need, how critical is the homogeneity of the opening? Can the opening be 50%?

Physicians do not ask these questions (do not request to support treatments for tumors of 3 cm or 350 cc vol). It is important to start clinical trials with robust systems to maximize the chances of treatment success. Researchers are trying to offer systems that provide faster treatment rates and treat larger volumes. Current devices can multiply the treatment rate by 4 while giving a homogeneous dose coverage. Each version will improve the intraoperative MRI imaging, especially T2*, that can validate the efficacy of the treatment and reduce safety concerns. When the beneficial application is found, the treatment flow and cost can be optimized. Getting out of MRI would be easier than getting into MRI.

5 Question to Dr. Ghanouni and all

What are the clinical applications and the ideal systems?

In an ideal world, the MRI system will allow coupling of the device that is filled with all the density of ultrasound elements that the system can fit in, with an imaging device that can identify the location of the lesion. FUS will have elements and supercomputers and can deliver the ultrasound conformal treatment around the lesion regardless of intervening bone, bladder, rectum, nerves, without contortion of the patient (no need to contort the pelvis, breast, etc.) in a one-size-fits-all. The physician can see the lesion, and treatment can be delivered per the doctor's order. There will be no need to monitor the treatment. It will be like radiation; physicians would know the sufficient dose that achieves the desired results. A PET scan is done later to check on the tumor. Parameters will be known, and the treatment delivered with no safety concerns and based on preoperative imaging. Physicians have safety concerns with the current systems.

Dr. Wood: "As much as I would like to believe that we can 'stuff things into a model' and solve problems with a magical therapy, physicians must fight against the desire to be perfect and to build the perfect system." The field needs to progress on a single line to show clinical benefit and value that makes commercial sense and integrate a reimbursement plan. Otherwise, things will take much longer.

Dr. Choy: This thinking should apply to many technologies. It is important to prove safety, efficacy, and clinical benefits, and obtain reimbursement; then move to an improved device. The ultrasound field is a target-rich environment, and it is important to hit these targets incrementally. The FUS field is advancing and adding use applications for the treatment of tremors and bone metastases and continues to hit additional targets. More clinicians should be able to use it in the OR and in other departments.

6 Question to all

What can we learn from other fields for faster implementation?

Dr. Wood: It is important to realize that not all scientific questions coalesce and align with translation. Researchers should learn from other disciplines and other energy applications. For example, there are many ways to approach oligometastatic disease or locally confined tumors in many organs. Many different technologies and choices are available, including image-guided radiation therapy, laser, photodynamic therapy, cryotherapy, etc. Advancing the field requires learning from past failures and learning how researchers can move fast. Urologists move quickly into technologies. Disciplines such as cryotherapy vs. microwave in the kidneys, each organ has its applications, each technology has phases of development. A lot can be learned from clinical sciences in different disciplines, coalescing with commercial actors in similar fields and outside communities to solve problems.

Dr. Choy: FUS should achieve similar status to radiology or imaging, microwave in kidney, cryotherapy, etc. Diagnostic ultrasound (such as computed tomography [CT] or MRI) is an essential tool in practice; it has a proven safety, consistency, and results regardless of the vendor. Similarly, physicians should trust that FUS achieves the desired results and can be operated by a trainee.

Left to right

Elisa Konofagou, PhD
Andreas Melzer, DDS, MD
Pejman Ghanouni, MD, PhD

Right

Yoav Levy, PhD



Dr. Wood: It is important to have a closed loop that anyone can do. Standardization will be important for trust.

7 Question to Dr. Melzer

What technologies should be developed through all phases, from planning to targeting and assessment of the treatment or other intended effects?

We need efficiency to reduce the need to monitor effects on the go. It took a lot of trial and error to learn the dose needed in radiation therapy. I am trying to set up PET MRI with ultrasound. If ultrasound can be used in conjunction with MRI to understand how long we need to sonicate, at which energy level to sonicate, and then move to more efficient radiology settings in certain areas and tumors, we could show the results more efficiently.

With regard to targeting, acoustic radiation force imaging is an important tool. Researchers should team up with imaging companies. A good example of an MRI company is Siemens Healthineers; their teams are working with clinicians and have prioritized acoustic radiation force imaging. We should communicate to these companies the need to get ARFI - Acoustic Radiation Force Imaging at more sensitive levels to use it for targeting, which will improve temperature mapping. We need to get a better understanding of what happens at the exact spot.

With regard to monitoring, clinicians need to get a precise understanding and a comprehensive assessment of what happens after sonication and be able to evaluate the achieved effects. PET can be used here, although I am not aware that patients treated with ultrasound are integrated in this schedule. Physicians and scientists with access to PET MRI should convince nuclear medicine people to develop better monitoring assessment techniques for targets and tumors treated.

Dr. Konofagou: We learned from ultrasound that monitoring can be done in real time. There are different effects that can be instilled in the brain, such as radiation forces, temperature, blood flow changes. The fMRI could be potentially used, as well as FUS, cavitation, and mapping. The advantage is that we can do all these together in real time, in tandem working confocally. It is challenging in the brain but can be done in other areas.

8 Question to Dr. Levy

What is the perfect treatment volume (200 cc or 1 mm³) and focus?

We should treat big volume but use high resolution to treat that volume. In that volume, we may have many types of tissues, and within the same tissue, areas that have different vascularity. The optimal solution is the one that has very high resolution (e.g., 1–3mm), that can scan, and has higher volume to cover whatever the physician requests. We need the smallest number to get the highest resolution and something with electrical steering that can work fast and cover big volume in real time.

Dr. Wood: Immunomodulation may be one aspect of the technology that can tip the face of oncology. With regard to volume, the field learned from experiments in the liver that bigger volumes do not achieve better outcomes. On the other hand, if researchers can identify neo-antigens in a tumor that can be targeted uniquely through FUS, and use feedback loops that the MRI can detect, that would be a paradigm-shifting, high-impact technology.

9 Question to all

Can you summarize your vision statement for the technology?

Dr. Hynynen: Go faster and better.

Dr. Woodworth: Having more clinical trials with standardized readouts, not just MRI readouts, is the way to go.

Dr. Wood: Leverage drug and device and image to mechanistically immune modulate or improve delivery of drugs already known to work in a way that is unique and impactful. Have a clinical impact and a road to clinical impact that drives every decision we make along the way.

Dr. Choy: Think how FUS fits adjacent to other technologies. For example, ultrasound can be one toolset next to immunotherapy, similar to RF ablation and other technologies. See how FUS fits into the puzzle and continue to focus on the targets where it is working (tremor) and improve on them to achieve trust.

Dr. Melzer: There is one MRI, and one ultrasound imaging machine for all procedures, but many dedicated FUS machines. Having multiplatforms, multimodalities, or multi-use FUS might be possible. It can be approved for certain indications, and this makes it easier to handle. These procedures require a lot of training and are not standardized, and this can be solved through multi-accessible FUS.

Dr. Levy: My vision is to accelerate to treatment. We have not reached the stage where we can use the technology when treatment is needed.

.....

Special Lecture

Reimbursement Through the Eyes of CMS

Thomas Scully

Former Administrator, Centers for Medicare and Medicaid Services



Thomas Scully

Former Administrator
Centers for Medicare and
Medicaid Services



View on the Foundation's
[YouTube channel](#) >

Foundation Council member Tom Scully is a general partner with Welsh, Carson, Anderson & Stowe, the most active U.S. private equity investor in healthcare. He was formerly the administrator of CMS, where he had an instrumental role in designing and passing Medicare Part D and Medicare Advantage legislation and initiated the first public reporting and disclosure for comparative quality among hospitals and other health care providers. To provide background about CMS and how it thinks about FUS, Mr. Scully said that, in fact, CMS does not think about FUS. CMS is a large organization with 6,000 full-time employees in Baltimore, 10 regional offices with about 50,000 employees, and 12 Medicare Administrative Contractors (MACs) that contract with CMS to run Medicare throughout the country. The MACs make a lot of coverage decisions, so FUS or any new treatment must be brought to the MACs.

The 12 regional MACs make many of the coverage decisions. If a MAC decides to cover a new FUS treatment under an existing code, that does not mean that commercial payers will also cover the procedure, and it does not even mean that Medicare Advantage plans (private Medicare plans) will pay for it. Generally, though, the private insurers tend to cover procedures that are also covered by Medicare because it is hard for them to say no if Medicare covers it. Medicare coverage gives private insurers an excuse to pay for a procedure, so Medicare decisions have become the leading edge. The first step in achieving coverage is often going to a MAC and making a case for a wonderful new treatment to replace a treatment that has been covered before with an existing payment code.

The reimbursement system is fair but complicated. It requires proof that a new treatment is better than an existing treatment. This is a high bar because everyone wants more coverage for everything, and everything is expensive. There is no shortage of physicians, practitioners, hospitals, and outpatient centers asking for coverage decisions. This creates the general feeling that CMS does not want to cover more things.

Procedures can be covered as inpatient, outpatient, or performed in a physician's office. These are three totally different pots of money, so there are three totally different processes for accessing each pot of money. Novel, hospital-based (inpatient) treatments for cancer patients are usually covered under existing cancer codes, especially treatments that fall under current Diagnosis-Related Groups (DRGs). FUS companies can also apply for a temporary (3-year) add-on code. If a company can convince CMS to make a national coverage decision because its treatment is so superior to other cancer treatments that CMS should carve out a separate hospital payment code for 3 years, the code is issued and tracked. CMS does not issue add-on codes very often, and once again, there is a very high bar for this. After 3 years,

if the data are good enough, CMS will add the new DRG and establish an initial payment rate for the hospital procedure.

The outpatient side has a separate coverage panel but similar process. New treatments are more easily covered when they fall under existing Ambulatory Payment Classification (APC) codes. When the treatment does not fall under an existing code, CMS can be convinced (with data) to issue a 3-year “pass-through” code, but these codes are difficult to obtain. After 3 years, a new outpatient APC code can be issued if the data show a substantial improvement for patients and there are good reasons why the new treatment cannot be covered under an existing code. However, CMS is moving heavily toward bundled payments for both inpatient and outpatient treatments. That is where CMS is going; it is the reason why CMS is hesitant to issue new codes.

The third coverage route is for procedures done in a physician’s office. It is based on the recommendation of an AMA RVS (Relative Value Scale) Update Committee (RUC). Companies must go to an RUC and argue that a new code is needed from a budget-neutral pot of money. CMS spends \$200 million on physician payments every year; adding a new physician payment and a new facility fee under Medicare Part B removes a payment from another physician and facility, so there is considerable hesitation for the physician community. It is a very complicated process but a fair process for CMS.

The people who work at CMS are fair but hesitant to add new payments and create change. It is not enough to say, “Look, we have a wonderful new technology...we have focused ultrasound driven by an MRI. Why don’t you pay for it?” The industry must show CMS officials why they, and the taxpayers, should pay for FUS. As a reminder, no one at CMS is thinking about FUS. Achieving coverage is a grind that requires a lot of time and attention, especially for procedures that require a separate payment rather than payment under existing DRG or APC codes. The overall trend for the past 15 years has been paying for bundles and bundles of bigger bundles. It is increasingly difficult to carve out special payments.

In conclusion, CMS likes new technologies, especially those that are significantly dynamic. CMS will add new payment codes and track the data, but it is a complicated hustle and a grind. It is not easy, but it is a fair process. CMS takes a taxpayer point of view. The process may be slower than the industry would like, but CMS is protecting the Medicare trust fund and making sure that the funds are used rationally, which is a good idea for Medicare beneficiaries.

Mr. Scully is happy to give advice about CMS and talk to members of the FUS community about CMS.

• • • • •

Special Lecture

Evidence Development for Medical Devices

Jill Hagenkord

Chief Medical Officer, Optum Genomics

In this special lecture, Dr. Hagenkord outlined the evidence and the evidence narrative needed to achieve widespread clinical adoption and reimbursement coverage for new medical devices from a private insurer's perspective.

It takes 14–17 years for a health product to move from concept to widespread clinical adoption and reimbursement. One reason for this long timeframe is the large amount of evidence that is needed to prove that a medical device is

- 1 safe,
- 2 works reliably and reproducibly, and
- 3 provides a beneficial outcome based on its intended use.

The time to widespread adoption can be lengthened by a medical device developer's lack of industry experience and unfamiliarity with the complexity of market access (e.g., research scientists and physicians who have only focused on their practice and/or academic practice). The first step, which gets skipped more often than one might think, is important. The company must determine: What is the device's intended use? Although it is common to develop a technology and then look for a problem to apply it to, the more successful route is identifying and characterizing a health problem and then developing a solution that best solves that problem. The next steps are proving analytical and clinical validity. The last step is proving clinical utility. Many companies waste time, money, and resources in the evidence development process by taking shortcuts, but companies that take shortcuts rarely succeed beyond some short-term wins. The clinical utility step is especially important for FUS and its specific intended uses.

Clinical utility is determined by payers, individual physicians, and professional societies. Validity studies provide the recipe for clinical utility, and there is not a lot of room for interpretation (i.e., "This is how you have to set up the study and these are the outputs that you have to have."). Clinical utility theory (what should be measured and the right study design) depends on a device's intended use, so there is not a one-size-fits-all answer. Determining clinical utility requires obtaining feedback early and often from clinical champions who can specify the right endpoints. Clinical utility development is the time to meet with stakeholders and seek feedback from payers. Consulting groups like Optum can help companies obtain payer and provider feedback, shorten the time to a coverage determination, and reduce the risk of being surprised that a clinical trial was not appropriately powered or did not answer a key question.



View on the Foundation's
[YouTube channel](#) >

The medical device development process requires solid early health technology assessment and effective clinical research. Companies should engage with medical experts during a device's earliest developmental stages. Engaging with technical key opinion leaders (KOLs) is crucial, even while working out the technical capability of a device and conducting validation studies. Engaged KOLs should be speaking at technical meetings, telling the story of the reliability and reproducibility of the technology. Before beginning clinical trials, companies must determine which key clinical champions and KOLs to work with and plan 2 to 3 years ahead to ensure that when the evidence is ready, the company is ready "hot off the press" to go to the right podium with the right KOL to tell the data story. Companies must start thinking about market access early in the process. They must evaluate the opportunity, the total addressable market, any competing technologies or devices that are being used at the same point in care, and the winnable market share. Data models can be used to predict whether a device is viable and worth investing time in.

Companies must think ahead about coding coverage and reimbursement. They should consult with reimbursement experts on the device type to understand the nuances of the type of coding, fee schedule, and downstream implications. Companies must speak with each payer and KOL one by one; it takes an entire team of people to go out with a nice, crisp evidence-based dossier and an effective narrative to go with that evidence dossier. Presentations must be made early and often, even when the evidence is not yet fully developed. The message must be, "I know I am only getting started on my clinical trial, but I wanted to give you an update on what we are doing...and this is when we anticipate it being done." Companies must constantly remind payers and KOLs about their product, how responsible they are being about their product, and their evidence generation process.

Payers include the 12 regional Medicare Administrative Contractors (MACs), the national CMS office, and private payers. Evidence review entities can provide evidence review, and some payers use them more than others. Private payers will usually negotiate their reimbursement rates based on some factor of the Medicare fee schedule, so the Medicare pricing determination has important implications for the commercial market.

In summary, it is not enough to have evidence. Companies must be able to articulate the story of the data and support each claim with evidence. The new technology must solve a real problem in medicine, fill a significant gap in care, and effectively impact a change in care when it reaches the marketplace. Finally, at the end of the journey, companies should watch the behavior of their device in the wild, identify any implementation blockers, and put resources toward unblocking any implementation gaps.

• • • • •

Overview

The Status of Reimbursement

Michael Broad

Data Strategy Director, Focused Ultrasound Foundation



Michael Broad, PhD
Data Strategy Director
Focused Ultrasound Foundation



View on the Foundation's
[YouTube channel](#) >

Dr. Broad outlined the basics of procedural reimbursement, explained why reimbursement matters, explored the landscape of FUS reimbursement around the world, and discussed the foundation's efforts to achieve further reimbursement of FUS procedures.

The Basics of Reimbursement

Achieving reimbursement requires regulatory approval, a billing code, payment levels, and coverage. Coverage occurs when a government or private insurer agrees to pay for a procedure. The payment rate is the dollar amount the treatment site and treating physician will be reimbursed after a procedure is covered.

Why Reimbursement Matters

Without sufficient coverage, patients must pay out of pocket or travel long distances to receive FUS treatments, which is cost prohibitive for most of them. Without a sufficient payment rate, the cost to a facility performing a procedure is not reimbursed. As a result, facilities can—and in the past, have—refused to provide a service. Without proven success in coverage and payment rates, the innovation of new devices or modalities is stifled.

The reason this matters to the foundation is that patients are effectively denied access to existing or novel FUS procedures.

The Coverage Landscape

The foundation maps the global coverage landscape. Reviewing the coverage map reveals that the number of reimbursed indications varies greatly between countries (e.g., Germany has seven indications that are reimbursed, whereas the United States has five, Canada has two, and China and Finland each have one). Looking at the indications that are approved but not covered paints a different picture and suggests the great potential for more covered indications in the future. In the United States, there are some states where all five indications are covered and others where only three indications are covered. In Canada, Ontario is the only province that has coverage (the coverage is for essential tremor and uterine fibroids). In Italy, there are some regions that are not covered at all; where there is coverage, it varies widely, from six indications in Lombardi to only one in Basilicata. Patients need to be made aware of regional and state coverage differences because the FUS community does not want patients going to be treated somewhere, only to discover that their insurance is invalid there.

Foundation Efforts in This Area

In Europe, the foundation's goal is to gain a more complete understanding of the continental reimbursement landscape. To begin to achieve this goal, the foundation has obtained detailed reports on the reimbursement of FUS procedures, including billing codes and payment rates for Germany, Italy, and the United Kingdom.

In the United States, the foundation is working to create awareness of net reimbursement processes to help treatment sites better understand how their payment rates compare with the internal costs of performing FUS procedures versus the standard of care. The foundation has held webinars and created a Cost of Care Calculator to achieve these goals.

On the advocacy front, the foundation's goal is to improve coverage and payment rates for FUS procedures in the United States. To achieve this goal, the foundation

- 1 submitted comment letters on a proposed Centers for Medicare and Medicaid Services pathway to reduce the lag time between FDA approval and Medicare coverage;
- 2 submitted comment letters proposing increases in the payment levels for prostate treatment; and
- 3 began robust advocacy efforts with G2G and the Medical Imaging Technology Alliance to identify champions in Congress and in the Veterans Health Administration to support enhanced coverage for veterans with prostate cancer, uterine fibroids, essential tremor, and Parkinson's disease.

The foundation produced a reimbursement strategy webinar series to show U.S. treatment sites how to better align the internal costs of performing FUS procedures. The goal is to improve payment rates. Dobson DaVanzo, a health economics and policy firm based in Northern Virginia, has been collaborating with the foundation in these efforts. Since this collaboration began in 2019, the mean cost values for billing codes in the program have increased 53%. Because these cost values will be used in the Medicare Cost Report to set future payment rates, these efforts should lead to positive changes in the future.

In conclusion, the lack of reimbursement and inadequate payment rates limit patient access to FUS procedures. Global coverage is incomplete but improving, with strong potential for expansion. Patients should be made aware that coverage can be regional. Understanding of the global reimbursement landscape is increasing, and device adoption and understanding of U.S. reimbursement processes has also improved. Advocacy efforts are helping improve coverage and payment rates in the United States (e.g., Medicare cost values have increased for relevant indications).

• • • • •

Cost of Care Calculator

Mark Carol

Senior Consultant, Focused Ultrasound Foundation

Dr. Carol presented the foundation's Cost of Care Calculator, a tool that he programmed in an Excel spreadsheet. The calculator allows users to select as many as six medical procedures and compare the true cost to perform the procedures with the commercial and CMS reimbursement amounts paid to perform them. Procedures can be selected from a database of more than 130 FUS and competitive alternative procedures (e.g., surgery, deep brain stimulation, other forms of ablation). Each medical procedure is characterized by approximately 30 variables.

The calculator determines how much a selected medical procedure will cost to perform based on literature-identified costing data. If desired, these data can be adjusted on a case-by-case basis using costs specific to a given hospital or facility. The calculator's payment rates are based on known rates for CMS and user-provided rates for commercial carriers specific to hospital contracts.

When the tool compares procedures, it creates a table that lists costs and payment rates by physician or facility along with additional factors, such as regulatory status and lost days from work or activities of daily living. The tool also allows users to compare the facility's net profit from an FUS procedure with the cost of lost MRI studies that could have been done if the MRI had not been used for FUS treatments.

The calculator is available for free from the foundation with minor stipulations. Users must be foundation partners or members. The calculator can be customized, but it is for internal use only. Partners' customers may only access a hard copy of the output. Users must also agree to share anonymous customer data with the foundation to make the calculator more accurate.

When it is opened on the screen, the Excel spreadsheet has the following tabs:

- | | |
|----------------------|--------------------------------|
| ■ Introduction | ■ Facility Costs |
| ■ Instructions | ■ Personnel |
| ■ Sheet to Duplicate | ■ Payment |
| ■ Procedure Database | ■ Wage Index Table |
| ■ Capital | ■ Geographic Adjustment Factor |



View on the Foundation's
[YouTube channel](#) >



Mark Carol, MD

Senior Consultant

Focused Ultrasound Foundation

Dr. Carol demonstrated the calculator using essential tremor for the example. He compared the costs of providing an FUS treatment versus deep brain stimulation versus surgery versus gamma knife. In another demonstration, Dr. Carol compared the payment levels for various prostate treatments.

The Cost of Care Calculator is useful to FUS manufacturers, treatment facilities, and treating physicians. A video that explains the structure of the tool and provides examples of how it might be used to promote the sale of FUS technology in a competitive environment is now available.

.....

Fireside Chat

Regulatory Strategies

Jessica Foley

Chief Scientific Officer and Managing Director, Focused Ultrasound Foundation

Laurie Clarke

Vice President and Principal, Medical Device Regulatory, TSG Consulting

Harold Stowe

Regulatory Consultant, TSG Consulting



View on the Foundation's
[YouTube channel](#) >

In this fireside chat, Dr. Foley discussed regulatory strategies for FUS device manufacturers with Ms. Clarke and Mr. Stowe. After a brief round of introductions and opening remarks, the consultants described TSG Consulting's medical device product development team and the company's range of services for various sizes of companies. The experts at TSG Consulting help device companies develop and implement regulatory strategies to meet their marketing objectives.

Left to right

Laurie Clarke, JD, MPP
Harold Stowe



1 What are the FDA's pathways for FUS companies?

The three primary routes for device approval are the 510(k) clearance pathway, the premarket approval (PMA) pathway, and the de novo device pathway. Examples from prostate ablation companies were used to further describe each of these pathways.

2 Where do you see FUS ablation now?

It varies by indication. Cancer applications will likely need to follow the PMA pathway. Other indications could include any of the FDA pathways. Some of the indications that began in the de novo category will now follow the 510(k) pathway. A company's marketing goals can impact the route that is chosen. After a device is put into the class III category, it stays in class III. A class III device cannot be a predicate device. (Device classification depends on the *intended use* of the device and also upon *indications for use*.) New indications with low-to-moderate risk are candidates for the de novo route.

3 How do consultants like TSG help companies?

TSG conducts regulatory research for each specific indication, provides cost-benefit analyses, breaks down the process into bite-size pieces, makes pathway recommendations, facilitates interactions with the FDA, and follows device companies through the entire process.

4 Has the FDA made any recent changes to its programs? For example, can you comment on the Safer Technologies Program for Medical Devices and the Breakthrough Devices Program?

The Breakthrough Devices Program is now 5 years old. It is a good but rigorous program. The reward is receiving more resources from the FDA and achieving approval faster. Interactive sprint reviews and the data development plans are additional benefits of the designation. Companies should apply for Breakthrough Device designation when they can demonstrate that they meet the criteria for the designation and before submitting a PMA, 510(k), or de novo application. If a first application for Breakthrough Device designation is rejected, a company can revise the application and try again.

5 In terms of timing, when should device manufacturers contact regulatory consultants?

It is best for companies to contact the consulting team as early as possible in the regulatory process. Ideally, companies should contact consultants before going to the FDA because the consultants can recommend the most appropriate timing for the first contact with the FDA.

The consultants welcomed the FUS community to contact them for any questions or for additional information.

.

Thursday, October 27, 2022



Thursday,
October 27, 2022

Special Lecture *FUS for Thyroid*

Brian Lang

University of Hong Kong



Brian Lang, MS, MBBS, FACS

*Clinical Professor,
Department of Surgery
University of Hong Kong*



View on the Foundation's
[YouTube channel](#) >

Over the past 7 years, Brian Lang and his team have treated more than 600 patients using FUS primarily for benign thyroid nodules. The Queen Mary Hospital and its associated sites in Hong Kong are among the most active areas today using the Theraclion echo pulse device.

Benign thyroid nodules, a common medical condition, can grow and cause pressure symptoms and cosmetic concerns. The standard of treatment is surgery, which is invasive and requires general anesthesia. Nonsurgical options include HIFU, RF, lasers, microwaves, or ethanol; all except HIFU require needle-based ablation, an important consideration for patients taking anticoagulants or antiplatelet therapy. HIFU can be performed on an outpatient basis and requires only 30 to 45 minutes in the treatment room. It also preserves organ function, requires no anesthesia, and is relatively inexpensive compared with surgery. HIFU has been shown to induce tissue necrosis and is useful for patients with large or growing nodules. Many different organs have been treated with HIFU.

The HIFU treatment device consists of a fluid-filled balloon to cool the skin, an imaging probe, and a treatment probe. An important consideration is the nodule location. If the nodule is close to the skin, HIFU can cause skin burns; if too deep, the energy can dissipate into other tissue.

To prepare for treatment, the patient must fast overnight and be in a supine position with the neck slightly extended. An ultrasound is done before treatment to locate the nodule, followed by local anesthesia and IV sedation.

The size of the nodule typically does not shrink much in the first 4 days after the procedure, but the color becomes more hyperechoic. Larger nodules normally need two treatments. Immediately after treatment, there is some redness on the treatment side due to cooling of the balloon and vasodilation.

The success of the treatment can be determined by measuring thyroglobulin before and 4 days after treatment. The nodules also become smaller, shrinking by 10% after a week, and about 50% after 3 months. A solid nodule will also have more cavitations. Moderately sized nodules will have about a 75% volume reduction after 6 months. Nodules with incomplete eggshell calcifications and intra-nodular macrocalcifications can also be treated. Recent data show that long-term efficacy is about 70%. Conglomerated or multiple nodules are more difficult to treat.

Shortcomings of the procedure include a longer treatment time compared with needle ablations, a possible unsatisfactory response or incomplete ablation in some patients, and potential complications and side effects (e.g., skin burn or color change, laryngeal nerve injury, Horner's syndrome).

In conclusion, ultrasound-guided HIFU is an effective and safe treatment for benign thyroid nodules. A session of HIFU ablation can induce significant nodule shrinkage and improve nodule-related symptoms. Other ablation techniques might be preferred over HIFU if more than one nodule needs treatment because of the longer ablation time required with HIFU.

1 How do you treat the entire depth of the nodule with the small focal zone length of about 5 or 7 mm?

The ablation is actually more than 7 mm because there is some heating both above and below the focal point. The depth is probably about 1.5 to 2 cm. For very thick nodules, we tend to do two sequential treatments.

2 How well do you work with endocrinologists in advocating for this approach?

We work closely with the endocrinologists. Many of our patients are referred by endocrinologists who are welcome to attend the treatment.

3 How do you work with patients to make the decision for HIFU versus RF ablation or surgery?

Only patients who are candidates for surgery but do not want it would get ablation. Some nodules may be more suitable for RF ablation, and some for HIFU. For example, HIFU is less suitable for nodules closer to the skin or very deep. Part of the learning process is selecting the right patient for the right procedure. For large retrosternal nodules, we would tend to recommend surgery. We would offer the minimally invasive procedure if patients were concerned about a scar or preserving the organ.

4 Are there any ultrasound characteristics that you identified on pretreatment or other ultrasounds that predict nonresponders?

Yes, looking at the pre-ablation ultrasound will indicate which patients will do better. Microcystic nodules tend to do better with thermal ablation. Vascular nodules are more difficult to treat, regardless of the mode of ablation.

.

Special Lecture *FUS for Diabetes*

Chris Puleo

GE Global Research



Chris Puleo, PhD

Senior biomedical engineer
GE Global Research



View on the Foundation's
[YouTube channel](#) >

Early in vitro work on stimulating peripheral nerves with ultrasound had shown that synapses were more sensitive to ultrasound than the nerve trunk. Researchers began looking at models using the end organ, where the synapses interface with the cells. This appeared to be a more precise way of doing peripheral neuromodulation. In preclinical rat models, the researchers attempted to tamp down toxin-induced inflammation in the spleen with FUS. In the first few experiments, a dose-response release of norepinephrine was obtained, indicating apparent sensitivity of the synaptic milieu to ultrasound pulses. The release resulted in an acetylcholine signal which led to the complete shutdown of tumor necrosis factor alpha (TNF-alpha) output. This effect did not occur in mice without T cells when the ability to release norepinephrine from the nerves was gone. The action appeared to occur through the cholinergic anti-inflammatory pathway.

Proof-of-concept experiments indicated that a mechanical effect was activating the nerves. Targeting different spots in the spleen had the same effect. When comparing the ultrasound response to that of electrical stimulation, the magnitude and decrease in cytokine output were the same with ultrasound stimulation, but without the cardiovascular effects of electrical stimulation. Vagus nerve stimulation, along with decreasing inflammation, also decreases hyperglycemia in animal models. Ultrasound activation of the splenic pathway did not have the same metabolic effect, so the researchers looked for an axon in the spleen that was stimulated by the electrical implant but not ultrasound. In looking at other neurometabolic points, the researchers focused on the porta hepatis, a site in the liver where the portal blood empties into the liver. Here, innervation to the hypothalamus sends the brain information about nutrients eaten. With ultrasound stimulation, although not much changed in the liver at the point of stimulation, key neurotransmitters in the hypothalamus were changed in response, including neuropeptide Y and pro-opiomelanocortin (POMC).

Preclinical work tested liver stimulation in type 2 diabetic rat models. The onset of diabetes was prevented with daily stimulation with ultrasound delivered for 3 minutes. When stimulation was stopped, diabetes markers increased. This effect was observed in genetic and diet-induced type 2 diabetes models. Although the porta hepatis had been considered for several decades as a potential therapeutic target for storing and using glucose, there had not been effective ways to activate it. Novel ultrasound therapy was tested in a manner similar to diabetes drug testing (e.g., oral glucose tolerance tests [OGTTs] and euglycemic-hyperinsulinemic clamps) in rat and pig models.

The molecular action of ultrasound was studied using a 3D model of neurons in culture to look for interactions with specific ion channels. Use of a transient receptor potential ankyrin 1 (TRPA1) blocker eliminated the ultrasound effect in both the in vitro and animal

models, supporting a hypothesis around mechanically activated Ca⁺⁺ channels. Additional observations across the neuroendocrine system showed that the ultrasound effects occurred in almost every organ.

The clinical feasibility of liver stimulation with ultrasound was assessed by several colleagues using different organs. A recently completed feasibility trial included 15 persons with type 2 diabetes. In this trial, most of the patients had their diabetes under control at baseline. In three who came in with diabetic glucose levels, levels decreased with treatment. The clamp data was more variable. Overall, the evidence was promising that the changes in therapy seen in rats may be similar in humans. Initially, the treatment appeared safe, which will allow the researchers to move on to the next steps and full pilot studies.

The researchers are also studying glucose and homeostatic model assessment (HOMA) effects of daily treatments at two sites, the liver and the gut, in animal models. Longer stimulus durations at two sites resulted in longer hyperglycemia remission after only a single treatment. Additional feasibility studies are ongoing.

1 Have you investigated whether there is an immune component controlling what you have seen, based on your initial observations?

We are doing ongoing work on pancreatic beta cell mass characterization and looking at immune cells. We expect to see a difference but wondered if this is also more nerve mediated.

2 Have you considered looking at other autoimmune disease to see whether this intervention can mitigate those diseases? Is it globally immunosuppressive?

Right now, the action seems to be nerve mediated and associated with particular neuroimmune pathways. We have not tested for actions on immune cells.

3 Did you try different patterns of stimulating the nerve cells to see whether you can create a different release or stimulation of the neurotransmitter?

TRPA1 is likely not going to be the only ion channel involved. Other researchers are looking at nerves that innervate the skin, which has different sets of ion channels that respond to ultrasound.

4 Is there a real requirement to do HIFU? It sounds like you do not need an FUS transducer, you could do it with basically a planar transducer placed over the liver.

Precision is key. In the liver, next to the porta hepatis, there are other variables that affect metabolism, so we need to know exactly what is being reached.

5 Could you ultimately see something like a wearable device?

A company called SecondWave is making what might be considered a wearable ultrasound device to apply energy to the spleen.

.

Pancreatic Cancer

MODERATOR

Joan Vidal-Jové, Comprehensive Tumor Center, Barcelona

PANELISTS

Jae Young Lee, Seoul National University Hospital

Eli Vlaisavljevich, Virginia Tech

Katherine Ferrara, Stanford University

Petros Mouratidis, Institute of Cancer Research



Joan Vidal-Jové, MD, PhD

Professor of Radiology
Comprehensive Tumor Center,
Barcelona



View on the Foundation's
[YouTube channel](#) >

Dr. Vidal-Jové observed that many mechanisms of treatments are being studied, including immunostimulation, histotripsy, and hypothermia. Almost all are intended to control either the tumor or the pain related to it. The pancreas is very sensitive and difficult to reach. This discussion will include how we guide therapy, whether full or partial ablation is better, response evaluations, drug delivery, and nanoparticles.

Dr. Lee is engaged in a study that has progressed to a clinical trial (60 people in the study) to determine whether mechanical treatment aids medical therapy. With implemented combination therapy, the response increased by 70%, which was also reflected in immunological samples. It is too early to know whether survival was improved, but quality of life is good. There was no problem with targeting, as indicated by no damage to tissues.

Dr. Vlaisavljevich has worked with histotripsy mostly in animal studies. Lately, his group developed tumor models to use with histotripsy, especially in tissue-selective studies. Histotripsy produced more immune biomarkers than thermal ablation. With cavitation, this is easier to detect. Thermal dosage is very important, and there is also the element of spontaneity. For these reasons, histotripsy was used instead of thermal ablation to kill cancer cells.

This group also studied pigs as a promising model to study our ability to target and treat using ablation and to determine the safety profile. The aim is to get complete ablation while preserving pancreatic structure. Quantifying the dose that causes damage in tissue is another area of research, as are strategies to return organs to their places after treatment. Pretreatment clinical trials have been done with a potential acoustic path. Ultrasound was shown to be good for treatment, but not for guidance.

Dr. Ferrara, comparing different treatment approaches, has worked with thermal ablation, incorporating CD40, which can be activated with drugs. Hyperemia surrounds the organ, and antibodies can activate the immune system. Markers seen in blood are related to type 1 interferons. Changes are seen especially with an adjuvant therapy given in addition to ablation, and those changes can be modified. Changes up-regulated in the blood are similar. Changes in trafficking of activated macrophages are being studied.

Dr. Mouratidis noted that the field has exploded. Within this turbulent decade, the field has progressed from thinking that the dermal stroma of pancreatic tumors was important, to thinking that the body creates dense stroma, to thinking that pancreatic tumors create dense stroma and cells. Using the last scenario, work has focused on how ultrasound will help increase the number of immune cells, namely by improving activated CDa+ cells in the tumor.

1 Questions to all

What are the results related to full versus partial ablation?

Dr. Mouratidis: The effects of ablation may depend on the model; in some models it may not be possible to liquefy all tumor tissue. Small animals are more fragile, and they tire and do not revive quickly.

Dr. Lee: Mechanical stimulation occurs at focus and pre- and post-focus areas, but there will always be residual tumor cells that remain inside or outside the tumor. Ablated cells could not be seen inside the pancreas itself. So far, no problems with mobility have been seen with ablation, and preclinically, safety profiles are positive.

Dr. Vlaisavljevich: Full ablation creates the maximum intended effect, although some investigators do not see the benefit of full ablation over partial ablation. The issue is not just partial vs. full ablation, but possibly reaching a volume that is too large. High-dose



Seated, left to right

Joan Vidal-Jové, MD, PhD

Eli Vlaisavljevich, PhD

On the monitor, attending virtually

Katherine Ferrara, PhD

cavitation would create bigger side effects. It is too early to say whether ablation can reduce the tumor to make it resectable, but there have been positive results related to an increase in resectability.

With combination therapies, the timing of combination therapies can be important. Are we to the point yet where we can say that we know that a certain order is best (i.e., FUS first or drug first)?

Dr. Ferrara: The established order is to start with a targeted treatment: ultrasound first, then histotripsy; paresis may be observed just after histotripsy. With a histotripsy/drug combination, it is better to start histotripsy as soon after the drug treatment as possible, but that depends on the drug being used. T cells must be primed and ready because thermal ablation effects occur so fast. Pretreatment shows definite improvement in results. Combination treatment has not been used to completely heat-fix the entire tumor, but issues with toxicity have not been seen. Many tumors express CDL1 regardless, so even nonspecific treatment will prime the immune system. Therefore, treat the tumor a few days before ultrasound therapy to prime the tumor cells. With combination therapy, the hope is to elicit more sudden changes in cellular effects, e.g., dendritic cell maturation. The right combination of immune modulators will produce more than just a local effect, and this can be bridged to the adaptive response.

What large animal work has been done on the feasibility of histotripsy for targeting tumors in pancreatic cancer?

Dr. Vlaisavljevich: In healthy patients, or those with a very small pancreas, magnetic resonance guidance and hypothermia are difficult to apply, although this was tried in the pig model at Virginia Tech.

Dr. Mouratidis: There is a role for ultrasound and histotripsy. Detaching the tumor from vessels is one challenge, but if we spend hours resecting the tumor, we cannot get all the cells, and then the tumor will return.

A lot of time has been spent on investigation of the abscopal (or off-target) effect. As we search for the right approach or combination of approaches for pancreatic cancer, can you share your thoughts on how to optimize the immune response to the treatment of this disease?

Dr. Vidal-Jové: Lymph node tissue is important because clearly lymph nodes drain the tumor, but if the tumor becomes big enough, it overtakes the lymph node. Tumor-specific antigen presentation might be used to model this. Also, injecting radioactive albumin could illuminate the path through the lymphatics. In other cancers, the antigen can be tracked draining from the tumor.

Dr. Vlaisavljevich: More T cells are seen in preclinical studies, but studies of antigen presentation are lacking in clinical studies to determine whether there is an immediate anticancer response.

Dr. Ferrara: CD4 T cells may be the important cell type. Most of the cells are ablated cells, so antigen is seen outside the cells, but it is difficult to detect specific antigens.

Damage-associated molecular patterns (DAMPs) would be self-antigens, indications of a problem but not necessarily uniquely expressed between cancer and healthy tissues. Therefore, there should be very few T cells that recognize them. DAMPs are mainly innate immune signalers rather than antigens themselves that bring in the advanced pancreatic cancer cells (APCs). Does immune modulation imply pro-inflammation?

Dr. Mouratidis: With combination therapy, we hope to more quickly change cellular effects, e.g., with dendritic cell maturation. With the right combination of immune modulators, we will see more than just local effects. We try to bridge this to the adaptive response.

• • • • •

Back Pain

MODERATOR

Wladyslaw Gedroyc, Imperial Healthcare NHS Trust

PANELISTS

Daniel Dux, University of Hannover (MHH)

Arik Hananel, FUSMobile

Lynn Kohan, University of Virginia

Viola Rieke, University of Utah



Wladyslaw Gedroyc, MBBS,
MRCP, FRCR

Consultant Radiologist
Imperial Healthcare NHS Trust



View on the Foundation's
[YouTube channel](#) >

Dr. Gedroyc briefly reviewed his and the panelists' work:

- **Dr. Gedroyc** used MRI guidance to target posterior aspects of the facet joints to destroy pain-mediating nerve fibers and reduce pain.
- **Dr. Dux** and his team improved upon the original work on facet joints and treated multiple patients.
- **Dr. Hananel** and his team are studying whether MRI guidance is needed to deliver FUS to facet joints safely, or whether a simple fluoroscopic technique can be used.
- **Dr. Kohan** is targeting sacroiliac (SI) joints with FUS
- **Dr. Rieke** is investigating neuromodulation to alter the perception of back pain.

1 Questions to Dr. Dux

Please tell us more about your work.

A problem with targeting the nerves that also innervate the back muscles is the possibility of hindering the patient's attempts to do physiotherapy to build back muscle strength. We targeted the facet joints, which is easier to do with HIFU than with needles because the target can be approached from different angles. Needles need to be replaced multiple times to treat the whole facet joint, and this is difficult. Our study participants were mostly self-referred, without having diagnostic blocks. The study included 70 treatments; 54% of the patients had clinically significant pain improvement. Those who reported improvement at one year reported 70% improvement.

Do you treat just one level? And both sides? Do you do MRIs beforehand to make sure the patient has no compressive elements?

The level depends on the MRI. We typically treat at S3 to S1; I think the highest level was L1. We treat both sides. And yes, we do MRIs beforehand.

Must patients have had a positive response to a facet intervention?

Not all patients. Most do not want to have infiltration beforehand. They want ablation because it is noninvasive, and the risk of side effects is low.

2 Question to Dr. Hananel

Please tell us about your philosophy of treatment and how you target the correct areas with fluoroscopy rather than MRI guidance.

Price structures, reimbursement, and changing targets and modalities created obstacles for adopting MRI, so we sought an option that was less disruptive while still providing value. We are using the same target as the standard of care for RF ablation. The only difference is that we switched from a needle to ultrasound, which provides a noninvasive, less painful approach. We can create slightly bigger lesions, so there is a higher success rate. The lesion is created from the bone–tissue interface, so the risk of having a floating lesion as with a needle is low. Targeting is easier. We dropped MRI guidance because it is expensive, and most pain clinicians do not have access to it. While MRI is a great imaging modality, we had a lot of incentive to replace it. We still use it afterwards to see the results, but fluoroscopy allows for an easier operation with good clinical results.

Daniel Dux, MD



3 Questions to Dr. Kohan

Please tell us about your work involving SI joints.

SI pain is very common and a good target for FUS. The innervation of the SI joint is complex. One of the challenges when treating the SI joint is that the nerve supply varies from person to person, and even within a person. Having a technique like FUS that allows a bigger lesion is beneficial. The innervation is also in multiple areas and involves multiple needles, which is painful. Having a technique to decrease pain during the procedure is beneficial. We started targeting this area in cadaver studies and found we could target the sacral lateral branches effectively without heating the foramen. We hope to start the process in patients

Does a posterior approach allow you to get less of the joint than you would otherwise? Is that a disadvantage?

We have only been able to approach the target posteriorly and cannot approach it anteriorly with any current technique. Emerging research is showing good longevity with regular RF, so we are expecting the same or better results with FUS.

Is it fair to say that we are looking for inspiration from approaches that have been done percutaneously and moving them into an interventional process?

Definitely. I think moving away from percutaneous needles to a totally noninvasive technique will be a huge advantage. Many patients are afraid of the needle procedure, which is painful and requires sedation.

4 Questions to Dr. Rieke

Please tell us about your neuromodulation approach to back pain.

Rather than destroying neural fibers, we are looking at neuromodulation as an option for resetting them to baseline to no longer produce painful outcomes. In one project, we are looking at the cervical spine and trying to develop an MRgFUS system for ablation, targeting the cervical facet joints directly or the medial branch nerves. We demonstrated safety in a goat model and are aiming to get FDA IDE approval for the first in-human trial. In a pig model, we used MRgFUS for neuromodulation of the dorsal root ganglion (DRG) to see whether we can get relief from neuropathic pain. To measure pain, we are working with a scale that is similar to the faces pain scale used for adults and children who cannot self-report pain. When we used FUS after creating a nerve injury, we saw a pain decrease about 3 to 4 weeks before it increased again.

How do you cope with not seeing emotion on the face of more "stoic" animals?

That is actually difficult. We treat one side of the pig and have the other as control and compare the responses. Some animals are more stoic. We are still reviewing histology samples to see how much neuritis developed. These are long-term experiments.



Left to right

Wladyslaw Gedroyc, MBBS,

MRCP, FRCR

Viola Rieke, PhD

Daniel Düx, MD

5 Questions to all

Have we decided whether we should be treating the facet joint itself or the medial bundle? Which is best?

Dr. Hananel: One of the main reasons we picked the nerve is based on reimbursement. In our experience, there is reimbursement for treating the medial nerve branch, and none for treating the joint. When we first discussed a pilot study with the FDA, they voiced a concern about joint stability if the joint itself is treated. I personally do not think this is an issue, but in terms of seeking regulatory approval, it can be easier to treat the nerve.

Dr. Kohan: From a clinical standpoint, articular injections have not shown the same longevity as medial branch nerve treatment. Treating the interarticular joint is falling out of favor in recent international guidelines for mediating pain.

Dr. Düx: There are advantages and disadvantages for both. It can depend on the patient. Some are active in sports and have strong musculature; targeting the nerve in them can upset the biomechanics of the spine and worsen their pain. Other patients are not very active, and their musculature tends to get fatty infiltration over time. It is much easier to target the nerve in them.

What other areas of low back pain do you think we should address?

Are there other areas for trying FUS?

Dr. Düx: Not much ablation is being done on the cervical spine because of the fear of hitting the nerve. With HIFU, targets can be reached more reliably. The ability to target higher levels would be an advantage.

Dr. Kohan: People with spondylosis can also have degeneration of the SI joints. In patients who have had fusions, the lumbar area can no longer be a target, and is a common area of pain for the SI joint.

Do you see any brain target indications for low back pain?

I'm curious how brain targeting for low back pain would differ from a chronic pain indication, for example.

Dr. Rieke: I'm working with an interventional neuroradiologist who is interested in identifying such targets.

Dr. Gedroyc: There could be some potential for cingulate gyrus or lateral thalamic neuromodulation.

My wife suffered from an epidural that went wrong and had severe spinal headaches for a few days. Could you speculate on the possibility of getting the same effect as an epidural but noninvasively using ultrasound?

Dr. Kohan: Epidurals are usually combined with a steroid to decrease inflammation. I would be more interested in targeting the DRG and finding out where the nerve root is being compressed.

Dr. Gedroyc: I think it would be very difficult to duplicate an epidural and would involve a long time in the MRI scan.

.

Soft Tissue Tumors

MODERATOR

Karun Sharma, Children's National Hospital

PANELISTS

Matthew Bucknor, University of California at San Francisco (UCSF)

Lynn Dengel, University of Virginia

AeRang Kim, Children's National Hospital

Pejman Ghanouni, Stanford University



Karun Sharma, MD

Director of Interventional Radiology
Children's National Hospital



View on the Foundation's
[YouTube channel](#) >

Dr. Sharma reported that, in a large experiment with desmoid tumors, patients responded well to FUS. Since 2010, research has dealt mainly with sarcomas. Prior to that, work with hypothermia hyperthermia and histotripsy showed promising results, although we need to improve the safety margin and prevent skin burns. Lessons learned with other therapies will benefit work with soft tissue tumors and vice versa, and the work done in animals will help us move forward.

Dr. Bucknor reported on a prospective clinical trial of FUS to promote immune responses in patients with newly diagnosed and metastatic undifferentiated pleomorphic sarcoma (UPS). Of the 86 patients treated with FUS, 55% had desmoid tumors. Tumors are larger and exhibit variability; response is the big question. The aim is to gain a higher level of confidence and improve patient outcomes. Clinical trials have been started involving pre-operative FUS in UPS combined with immunotherapy.

Dr. Dengel described a pilot evaluation of FUS ablation and FUS + PD1 antibody blockade in treating advanced solid tumors. The group wants to improve the tumor microenvironment by using partial FUS ablation to enhance tumor antigen presentation and T-cell infiltration.

Dr. Kim described a phase 1 trial treating pediatric refractory bone and soft tissue tumors with thermosensitive liposomal doxorubicin + MRgHIFU. Complete ablation is not possible, and lesions are not targetable with HIFU. In the future, hyperthermia and histotripsy applications will be tried in combined approaches with drug/immunotherapy/radiotherapy.

Dr. Ghanouni is engaged in a large clinical trial of many FUS applications; the trial enrolled 105 patients with desmoid tumors. A new, versatile MRgHIFU device has been developed for treatment of musculoskeletal tumors. Existing systems were designed to treat abdominal fibroids, which means considerable time is spent recalibrating the system. In addition to equipment limitations, there are tumor limitations. Challenges include positioning the patient (involving much variability and time), skin and nerve protection,



AeRang Kim, MD

and size limitations that prevent treating large tumors in one session. Long-term thermometry is required to accurately calculate total thermal dose. The field is transitioning, and new devices must be integrated into a new system.

1 Questions to all

How can the treatment of soft tissue tumors be expanded?

What is needed to deal with equipment limitations and tumor limitations?

Dr. Bucknor: Different effects occur across different tumor types, which requires a more exhaustive and organized approach. There are so many kinds of tumors, and so many different imaging characteristics with likely different responses for each. In addition to tumor heterogeneity, issues include location in the body, how the tumor looks, and equipment limitations. This requires a more exhaustive and organized approach to an exponential number of possible treatments. Treatment may result in some pain relief, but the tumor will likely recur, and the patient will need another treatment.

Dr. Dengel: The parameters for treatment must be defined at the outset, e.g., ultrasound-guided ablation must be deeper than 5 mm under the skin. One approach is to ablate one-third, two-thirds, or all of the tumor, but that must be decided in the beginning. In general, the goal is to ablate as much of the tumor as possible, so the clinician may have to plan for several several-hour treatments, including reimbursement and accumulated doses.

Dr. Sharma: Anesthesia is a concern, especially for pediatric patients (currently limited to 4 hours).

Dr. Kim: Solid tumors are still systemic diseases.

How do you address the heterogeneity of soft tissue tumors?

Dr. Bucknor: Mechanisms to enhance drug delivery can be combined with immunotherapy. Like ablation alone, immunotherapy will not cure metastatic cancers, but FUS can do that in a combinatorial approach.

Dr. Dengel: An immunogenic peel can be created around the ablated core.

Dr. Kim: Combination therapy introduces challenges and limitations such as unreliable imaging—results are not predicted by what you see, and you see a lot of heterogeneity.

Dr. Ghanouni: Desmoid tumors can be controlled, but investigators are not confident that they can treat premalignant tumors before they metastasize. Early immune readouts look positive. Combining FUS with other treatments could improve long-term outcomes with partial ablation.

How do you get reimbursed successfully by insurance when treating soft tissue tumors?

Dr. Ghanouni: It is very hard to get initial approval for FUS and equally hard to get approval for follow-up.

Dr. Bucknor: Desmoid tumors, for example, often need to be retreated. UCSF, where they moved FUS equipment from an isolated clinic to a hospital center, has had positive experiences with reimbursement so far.

Pejman Ghanouni, MD, PhD



Dr. Ghanouni: The general difficulty in getting FUS treatments approved for reimbursement impacted some investigators' decision to switch to cryotherapy, which is easier to get approved. Also, it is relatively easy to get approval for treatment of children. Much of this issue is familiarity: most clinicians know about cryoablation, but few know about FUS.

What devices are being used and what are the current limitations (including technical limitations)?

Dr. Ghanouni: It is difficult to position body parts, particularly hand or foot, for FUS treatment, but better-designed equipment will help. Currently, the equipment is tethered to the table, so the first order of business is to enable removing its attachment to the table and putting it onto a robotic arm.

Dr. Kim: All patients are under general anesthesia but positioning them is still a lot of work. In addition to getting the patient on top of the transducer, the patient has to stay in that position for a few hours, so it is important to make sure that every pressure point is cushioned.

How should we talk to the patient about the treatment plan?

Dr. Bucknor: *How* to talk to the patient depends on the goals of treatment for the particular patient. Treatment design focuses on the patient's goals for care. Moreover, the patient is often involved in getting approvals.

Dr. Ghanouni agreed with Dr. Bucknor.

.....



Karun Sharma, MD

Liver

MODERATOR

Joan Vidal-Jové, Comprehensive Tumor Center, Barcelona

PANELISTS

Mishal Mendiratta-Lala, University of Michigan

Zhen Xu, University of Michigan

Katherine Ferrara, Stanford University

Eli Vlaisavljevich, Virginia Tech



Joan Vidal-Jové, MD, PhD

Professor of Radiology
Comprehensive Tumor Center,
Barcelona



View on the Foundation's
[YouTube channel](#) >

Dr. Vidal-Jové. Liver tumors are the most representative in treatment methodologies: 43% of oncology treatment is for liver cancer. Methods include thermal ablation, hypothermia, histotripsy, and drug treatment.

Dr. Mendiratta-Lala. She runs the clinical trial, Hope for Liver (HFL), in Michigan. Results are still accumulating and being analyzed for the 46 patients they treated with histotripsy. Many patients had diffuse metastatic disease, but in this trial, they treated only one to three lesions for each patient. They successfully dealt with tumors close to the capsule and had positive results. For the HFL trial, histotripsy was used with the premarket model. Investigators did not have to deal with rib issues but developing a new device would make the intracostal approach easier. Each patient was under general anesthesia, so the motion of breathing was not an issue. All safety endpoints were met, and all patients are still alive for the 1-year follow-up.

Dr. Xu. Tumor stage is a big factor, and these researchers look at the shape and size of the tumor when considering treatment delivery. Some data show that histotripsy can have a substantial effect on immune response, but studies have not been done to determine safety. Most patients in the liver trial have multiple tumors at an advanced stage, so investigators may have to combine histotripsy with immunotherapy. With late-stage therapy, you are trying to treat the entire liver. The difference between heparin injection to study excessive bleeding post-treatment was studied statistically. Intracostal treatment uses subcostal ablation, so they do not have to go through the ribs. Rib-heating was consistent and below the threshold temperature, and results show no difference.

Using the rat liver model, researchers tracked intrahepatic metastasis after 2 to 3 weeks, after treating 50% to 75% of the tumor volume. All had tumor-free survival to the endpoint of the study, and histology confirmed that there were no tumor cells.

Dr. Ferrara. The focus for these investigators was use of radiology and ultrasound in pancreatic and breast cancer, as well as studying mutant gene delivery in the liver. If immunotherapy proves successful, they will add ultrasound and an additional drug in an

effort to get around regional disease. Microbubbles and plasmas have been used to increase antitumor effects. The group also looked at gene delivery and associated viruses trafficked to the liver. Next, they will transfect different sections or cell types in the liver.

Dr. Vlaisavljevich. Challenges in the use of histotripsy include targeting. This group is developing anesthesia to ease focusing issues and wants to ablate various types of tissues as well as study ex vivo and in vivo patients in the first feasibility test. If a more fibrous tumor, e.g., a cholangiocarcinoma, is subjected to histotripsy in the organ, the optimal dose must be determined. Some tumors could take at least 4 times the dose, which suggests that many patients are being over- or under-treated in the effort to achieve ablation. Caution is needed when ablating tumors close to the liver capsule or even through two lobes of the liver. In addition, clotting around a major vessel should be monitored. Treatment devised for liver cancer may also be used to treat gall bladder and stomach cancers.

Seated, left to right

Joan Vidal-Jové, MD, PhD

Eli Vlaisavljevich, PhD

On the monitor, attending virtually

Zhen Xu, PhD

Mishal Mendiratta-Lala, MD

Katherine Ferrara, PhD



Left to right

Joan Vidal-Jové, MD, PhD

Eli Vlaisavljevich, PhD



1 Question to all

Should we treat all the lesions in the liver? Partially? In combination with other therapies?

Dr. Mendiratta-Lala: Whether all the lesions in the liver should be treated at once, treated partially, or treated in combination with other therapies is a question of timing. More data are needed, but we are moving beyond the 3-mm tumor in efforts to find the safe size.

Dr. Xu: Treatment may depend on the stage of the tumor. Early-stage ablation can be used, but we do not have enough data to know the largest tumor that can be treated in one session.

Dr. Ferrara: For patients who have many tumors, multiple ablation treatments may not be possible, but some sort of combination may be possible.

Dr. Vlaisavljevich: There will definitely be cases where treating the whole liver is not practical. The liver is a huge duct-filled organ with a consistent parenchyma.

.....

Prostate

MODERATOR

Clare Tempany, Harvard University

PANELISTS

Rajiv Chopra, 8Fold Mfg LLC

Karen Cornett, Sonablate Corp.

Behfar Ehdaie, Memorial Sloan Kettering

Hugo Embert, EDAP TMS

Pejman Ghanouni, Stanford University



Clare Tempany, MD

Ferenc A. Jolesz MD Professor
of Radiology
Harvard University



View on the Foundation's
[YouTube channel](#) >

In a brief overview, Dr. Tempany said that HIFU with ultrasound guidance is now the most common ablative technique reported in the literature for focal therapy of prostate cancer; 27 studies are now in various stages of development. In the last 10 years, MRI has enabled lesion definition of aggressive prostate cancer. Four companies have received FDA or Conformité Européenne (CE) Mark clearance for ultrasound ablation of the prostate.

1 Questions to all

The adoption of HIFU for prostate cancer is still very driven by patients worried about whole gland therapy. Do you think this will pivot to become more physician-driven?

Dr. Embert: From my point of view, the earlier the better—but it is a difficult paradigm shift. The progress in imaging, especially with MRI, has proven to play a significant role in diagnosis. Some additional Level I evidence may be needed. Several randomized controlled trials are in progress, comparing focal therapy to active surveillance or robotic prostatectomy. We hope the results will help focal therapy become a standard of care.

What are you telling the physicians now, relative to marketing and reimbursement?

Dr. Embert: Reimbursement is a huge driver. It helped to get a Current Procedural Terminology (CPT) Category I code for transrectal application of HIFU, and to have Medicare set an appropriate payment rate. Coverage is still needed from insurance companies, which rely on the guidelines.

Ms. Cornett: Reimbursement has been a limiting factor, but we are on the cusp of focal therapy becoming mainstream. I think we are headed in the right direction, and the guidelines will catch up soon.

Dr. Ghanouni: All of our patients have been covered by Medicare. Prior to the code changes, some paid cash, but this has largely been eliminated.

Please tell us about the interest level of your urology colleagues in using focal therapy, and how young urologists are being trained in this area.

Dr. Ehdaie: Prostate cancer is still the leading cause of male single organ cancer in the United States. We know that 50% of men diagnosed through screening have low-risk or low-volume prostate cancer, so the number of candidates for focal therapy is high and continuing to increase. Although the concept of focal therapy is not new, the urology community is slow to adopt it because of the classic barriers that have always obstructed minimally invasive procedures. We now have better techniques to detect prostate cancer with image-guided biopsy. As a community, urologists know that 75% of men with low-risk prostate cancer are being enrolled in active surveillance, which is astonishing. Our patients are now anchored to the concept that prostate cancer in many forms is not lethal, and that quality of life is more important. We cannot take a step back. To tell a patient that he has now “fallen off a cliff” and needs an entire organ removed or radiated is unacceptable. Focal therapy needs to demonstrate that there is a clinical benefit to the patient without a significant harm. My belief is to keep men on surveillance without the need for radical treatment or radiation therapy as long as possible. We can extend patients’ quality of life without jeopardizing their long-term outcomes.

Tell us about your experience with avoiding side effects and how you handle preservation of the neurovascular bundles, urethra, sphincter, etc. during your transurethral and transrectal therapies.

Dr. Ghanouni: To add to Dr. Ehdaie’s comments, about 40% to 50% of men undergoing surveillance move out of surveillance after 5 to 10 years and need some kind of therapy. Taking them from surveillance all the way to whole gland radiation or prostatectomy is a big jump. Thankfully, we have an intermediate tool. Many patients seeking this technology have done their homework and been fortunate to talk with an open-minded urologist to review the limitations of surgery and radiation, which cause a lot of problems for patients. We have done multiple studies to show that the focal alternative is safer. The onus now is on showing efficacy. Right now, it hovers around 80% over 1–5-year follow-ups. Raising that number will help with adoption and demand.

With about 15 years of data now, how do we get the guidelines changed to accept focal therapy, rather than saying “clinical trials are pending”? How much data do we need?

Dr. Chopra: I think the guidelines are tied to utilization; the technologies need to be used more. With 27 clinical trials on HIFU in prostate cancer, I am not sure how many more trials are needed. In the world of urology, many technologies (e.g., proton therapy, radiation therapy) are tied to business models. If HIFU does not have the same approach, it will not be competitive.

Dr. Embert: The word “experimental” has been written in every guideline around the world when referring to focal therapy. The guideline writers underestimate the impact of this word on making the technology available to the patients. As far as data, I am hopeful that the two or three randomized clinical trials now in progress will help with moving the



Left to right

Clare Tempany, MD

Hugo Embert

Pejman Ghanouni, MD, PhD

Karen Cornett, RN

Behfar Ehdaie, MD, MPH

guidelines toward a more favorable statement. This year, for the first time, the American Urological Association (AUA), updated its guidelines for localized prostate cancer with a far more favorable statement for ablation for intermediate-risk prostate cancer patients. The word “experimental” was not used.

Dr. Ehdaie: I’m an optimist. We should probably do a study to look at the history of active surveillance and how it was adopted into our guidelines. At the moment of adoption, active surveillance eliminated 30% of radical prostatectomies and radiation treatments in urology groups and academic centers. Initially, the literature supporting active surveillance was based primarily on retrospective long-term data, but it was led by centers of excellence. The banner of quality of life was waved. This model goes against the concept of financial viability as a requirement for adoption. We have been resistant to focal therapy that, from both a financial and data perspective, is as far along as active surveillance.

Dr. Ghanouni: As mentioned earlier, the HIFU focal procedure now has a code that got AUA support. We need to broaden those efforts. I do not know if more randomized controlled trials will help move the dial or just lead to more arguments about how they were done. Looking at examples from other applications, there is always something to quibble about.

Dr. Embert: For active surveillance, a randomized controlled trial was pivotal for allowing the guidelines to evolve. It was not even a successful study; it failed to enroll and recruit, and the follow-up was not as planned. But at the end, the survival curve did not show much difference between patients who received no treatment and those that had a radical prostatectomy. However, the “box was checked for RCT.” We now have long-term data for safety and efficacy and need to check the box to make it to the guidelines.

What are your thoughts about focal ablative techniques for benign prostatic hyperplasia (BPH)?

Ms. Cornett: Our company looked at BPH first. After seeing that treating benign tissue was effective, we transitioned to cancerous tissue. I think the approach has not been studied further because of the cost issue. Patients who fail standard BPH treatments are looking for something else, so I think we will start seeing more clinical trials with HIFU. From a commercialization standpoint, it makes sense to have one device that can treat two different conditions. I am not sure whether it makes sense for this country, but it may for others.

There are several different approaches for doing the procedure, i.e., transrectal, transurethral, and transperitoneal. What are your thoughts?

Dr. Ghanouni: Basic considerations include a combination of the gland size, which can impede approaches, calcification distribution, and the location of the cancer. For an anterior lesion, especially in the larger gland, we will probably use a transurethral

Left to right

Karen Cornett, RN
Pejman Ghanouni, MD, PhD
Hugo Embert



approach if calcification is not in the way. For a posterior lesion in a smaller gland, a transrectal approach could be used with either ultrasound or an MR-guided approach. For a bigger gland, we would probably use a transrectal approach with MR guidance.

Dr. Ehdai: I am wondering why we cannot have consolidation in this area. A single company can provide all of these services and may have leverage against companies working against each other for a smaller portion of patients. As far as reimbursements, we are moving toward bundled payments that consider the lifecycle of the patient from diagnosis to death. From that perspective, focal therapy should be inviting to both the institution, because of outcomes, and the payers, because of costs.

Dr. Tempny: Many of these therapies can be done in smaller clinics and not major care centers.

Are there other adjunctive therapies (chemotherapy, immunotherapy, low-dose radiation) that could be combined with MR-guided ultrasound or ultrasound-guided ablation?

Ms. Cornett: This is starting to be studied in the U.K. One trial is looking at treating index lesions in patients with metastatic disease and then following up to see whether radiation is needed. Another multiarm trial is looking at focal therapy combined with adjunctive therapies.

Dr. Ehdai: I think we must first define where we are failing with focal therapy. We may be able to improve outcomes by such things as expanding our treatment area, improving our imaging, and receiving real-time feedback during treatment. Adding systemic treatments changes the risk group of patients. A patient with metastatic disease will ultimately fail systemically. However, focal therapy could be useful in settings with metastatic disease. The benefit will be a clinical one, in which the duration of treatment is much shorter. I think there will be a role for focal therapy combined with systemic treatment in patients with metastatic disease. Or at least it will be studied.

We still have a lot to learn about recurrences and residual disease. PET will probably help target local recurrences. Prostate-specific membrane antigen (PSMA) therapy appears to be working for metastatic disease. What has your experience been when looking at modalities other than MRI?

Dr. Ghanouni: We have used PSMA in part for screening purposes if we are concerned about a risk for extra-prostatic disease or other risks. PSMA has limited sensitivity. In one case, a patient had a local recurrence in the prostate as well as a positive node 10 years post-radiation. The MRI was almost uninterpretable 10 years post-radiation. We ablated the prostate recurrence and PSMA helped us with localization. We were able to radiate the node, and the patient has done well. So, there are roles for some of these other techniques.

• • • • •

Registry Panel

MODERATOR

Mathieu Burtnyk, Profound Medical

PANELISTS

Katie Gant, Insightec

Karen Cornett, Sonablate Corp.

Matthias Baumhauer, Mint Medical



Mathieu Burtnyk, PhD

Senior Vice President Product Leader
Profound Medical



View on the Foundation's
[YouTube channel](#) >

Dr. Burtnyk said that clinical trials must be done to get to the production stage, but for that, feedback from real-world use is needed, and registries provide information on real-world usage for new technologies. This group does preclinical and clinical trials. Establishing a registry is very expensive, and 10 years is a long time to get data. Additional considerations are administrative overhead and funding. Examples include the international registry called CARE, the COLD registry for prostate ablation, and the HEAT registry. (SPARED never got off the ground because of data-sharing problems.) Manufacturers have a role in gathering and sharing data with the community, but a sponsored registry may incorporate bias. Ownership motivates and brings treatment ideas and methodologies to life. The question is when to transfer that ownership from the manufacturer to the medical community. Registries are important to bring medical technology to the masses, and then reimbursement becomes an issue.

Dr. Gant highlighted that the goal is to create a structure for real-world data, but the infrastructure to do that is not yet in place. Another consideration is what happens after the registry is in place. To get people access, Insightec has shifted from time-to-market-the-technology, to time-to-value-the technology, i.e., how to provide value to each stakeholder. Most important is the patient, family, and friends. Becoming the standard of care entails thinking systematically to include the established players and stakeholders.

Ms. Cornett. Sonablate has a Current Procedural Terminology (CPT) and is well along to standard of care. Although nay-sayers will persist, it is important for manufacturers to be able to say they believe in data. Sonablate has compiled an HIFU Evaluation and Assessment of Treatment (HEAT) registry, a web-based platform to store clinical data.

Dr. Baumhauer noted that aggregated data bring added value, which alone establishes the importance of registries.

1 Questions to all

The adoption of HIFU for prostate cancer is still very driven by patients worried about What are the challenges to overcome in both setting up and executing clinical registries?

Ms. Cornett: The U.K. clinicians are reimbursed if they maintain a registry. But regulations differ among jurisdictions, for example, whether patient consent is needed. First, keep the registry small, get buy-in from stakeholders, and then expand. The design of the platform and the registry itself are fundamental to getting high-quality data. Custom-tailored software tools may be more useful than a more standard structure.

Dr. Gant: Using data collected from patient-reported outcomes is a way to implement patient engagement. This is an opportunity to engage with the patient and bring the patient's voice into the research, e.g., with quality-of-life data or diary information. In addition, we should try to harmonize the research environment across different disciplines.

Dr. Baumhauer: Data governance and data sharing are organizational issues.

What lessons can we learn from successful registries, whether in FUS or other therapies?

Dr. Gant: First, we need to understand what a registry is and whether it is the right tool for the current job. Registries and clinical trials are really part of the same thing. Registries may allow you to come up with new hypotheses to explore. We can learn from registries, and we can standardize how they work, so the more systematic and standardized registries are, the easier it is for the community to make systematic improvements.

Katie Gant, PhD



Left to right

Mathieu Burtnyk, PhD

Karen Cornett, RN, MSN



Ms. Cornett: HEAT registry data are impactful in showing that FUS, rather than treating the whole gland, is effective. Learn about patients from physicians who have used particular methods.

Dr. Baumhauer: Data entered into a registry may be used for another purpose—it is an organic situation. Collaboration is essential to create a community to evaluate procedures. Investigators may not have enough data from their own research for what they want to study. At the same time, they can learn from each other.

Dr. Burtnyk: Registries can be challenging and complex, but they do bring quality to the field. If you do the up-front work, it pays dividends 10 to 15 years later.

.....

Special Lecture

Addressing Disparities in Clinical Trials

Freda Lewis-Hall



Freda Lewis-Hall, MD

Former Executive VP, Chief Medical Officer, Chief Patent Officer
Pfizer



View on the Foundation's
[YouTube channel](#) >

Dr. Lewis-Hall is a clinician, a researcher, a leader in the biopharmaceuticals and life sciences industries, and an advocate. She said that the goals of clinical trials have always been safety, efficacy, and effectiveness of outcomes, but in the past, those enrolled in clinical trials did not necessarily represent the people most affected by the tested conditions and diseases. By 2020, the percentage of women had increased to ~53%, but not so for race/ethnicity: 75% were white, 8% Black, and 11% Hispanic. Some 30% of participants were over 65. She listed the barriers to increasing diversity and presented solutions.

Barriers

- **Lack of representation.** The research ecosystem itself is a source of bias. Formulation and dosing must be modified for different types of patients, e.g., for children or Asians.
- **Logistics.** Researchers are deployed to clinical trials by sites, but often those sites are not accessible to the full range of the community, e.g., rural areas. Logistics are designed-in that require patients to travel great distances to comply with the required treatment. Remote monitoring and other technologies could make the clinical trial more accessible.
- **Awareness.** In the community, lack of awareness of clinical trials in general and of specific trials is a significant barrier.
- **Trust.** To address past atrocities and convince prospective participants of their safety and rights protection, we need to engage the communities about their lack of participation.

Solutions

- **Data.** Include data on particular barriers and challenges (for example, lack of an elevator to access a clinic) and apply that data to develop protocols.
- **Logistics.** Address logistics of awareness (i.e., why people do not know about a particular trial, and about the clinical trial process in general) and how to make people aware.
- **Trust.** Address mistrust in the system. Do not approach the community only when you need participants for a trial but treat the research aspect as part of clinical care in general. Also include community members on advisory boards or on an IRB.
- **Trusted intermediaries.** Engage trusted intermediaries in the community (e.g., a pharmacist or nurse who has served those people), so people know the clinical trialists are there as part of the overall health care system.
- **Collaboration.** If we have assessed the epidemiology correctly so we can describe the patient population, we can establish collaborations and partnerships to build a system that promotes widely available health care. Ideally, this system will meet both prevention and treatment needs, thereby delivering better health care to individuals for better health outcomes to the population.

.

Gene and Cell Therapies

MODERATOR

Bob Smith, Pfizer

PANELISTS

Russell Cruz, Children's National Hospital

Natasha Sheybani, University of Virginia

Isabelle Aubert, Sunnybrook Research Institute, University of Toronto

Hong Chen, Washington University in St Louis

Nick Todd, Brigham and Women's Hospital



Bob Smith, MBA

Senior VP, Global Gene Therapy
Pfizer



View on the Foundation's
[YouTube channel](#) >

The panel started by an introduction by each of the panelists.

Dr. Smith developed a gene therapy program that has direct application to use with FUS in rare diseases. Collectively, rare diseases are common, but individual diseases are rare. Those afflicted are a heterogeneous group. Most rare diseases have a genetic origin, but the etiology of the disease is not understood. Infants and young children experience significant morbidity and mortality.

These investigators want to treat an underserved population by applying new technologies. Gene therapy is an attempt to replace a damaged gene with a correct copy via a viral vector. It is potentially one-time treatment. With in vivo gene therapy, the gene is introduced systemically or by direct injection. There are also gene-editing approaches and gene regulation approaches. Viral-based therapies could be ongoing.

Dr. Cruz has worked on cell-based therapy for the treatment of opportunistic infections, including HIV. Introduction of cell-based therapies starts with a cell source, either from the patient or a donor. The cells are processed, expanded, and reinfused. The two main immune effector cells are T cells and NK cells. The T cell recognizes cells on the inside; the NK cell recognizes cells on the outside as well. They can be modified for the specificity needed. Molecular immune therapies in general are more active than passive cellular immunotherapy. With gene therapy and stem cell therapy, the effects must manifest in the patient, so the investigator is not following the cell per se, but the cell's activity, and this can be combined with FUS.

All methods are challenged to get to the right tissue, and to the right cells in that tissue. FUS aids with focusing them. In addition to opening the blood-brain barrier (BBB), they focus on making the tumor site more attractive to the cells, so those cells will stay in the tumor. Physical obstacles must be disrupted by the existing procedures. Another potential application of FUS could be to do the opposite, by coupling cells with caspase-9 or -8

Left to right

Russell Cruz, MD, PhD

Natasha Sheybani, PhD

Hong Chen, PhD



switch, thereby making a “remote control” to turn off the cell attraction of the tumor site with FUS and prevent off-target toxicity. Consequently, these applications will have applications in the manufacturing lab.

Dr. Sheybani has applied FUS in immunotherapy for CNS disease, either brain tumors or neurodegenerative disorders, which involve the BBB. An emerging application of FUS may be modulation of genetic circuits to influence gene expression within tissues. This involves both off-tumor and on-target toxicities.

Dr. Aubert works on neurodegeneration with gene delivery and cell delivery in large molecules. Gene therapy can be delivered with very localized invasive surgeries, e.g., in Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis. To move forward, their group is using what has been done with direct injection. Vectors are the adeno-associated viruses (AAVs) directed to the cells that transfer or pass the BBB. They are identifying the best combinations that can be done, e.g., astrocytes. Meanwhile, the technology keeps moving. Unmet needs include delivery to the brain via FUS, which is done noninvasively.

We can remove the capsid of the cell with HBKO so that gene delivery diffuses more and the HBKO initiates a cascade of immune response.

Dr. Chen wants to develop sonogenetics and the use of ultrasound in the nose/brain pathway to deliver treatment. They have also used microbubbles and AAVs. Opening the BBB with the FUS procedure has been proved safe. This is why intranasal delivery is so important. Given intravenously, safety is dose-dependent.

Dr. Todd has focused on gene delivery to treat Huntington’s disease. Clinical trials for administration of gene therapy are ongoing: Intravenously and via intrathecal injection or intraventricular injection, or direct injection into the brain or another organ. Peripheral organs are relatively easy to access. There is an issue with coverage vs. concentration, i.e., widespread coverage, but limited concentration. CSF is in-between and where you get a little of each. We need widespread coverage with adequate concentration.

1 Questions to all

Did you see tumor cells released into the blood after BBB opening?

Dr. Chen: When trying to target brain tissue specifically, they did not see tumor cells released into the blood. Preclinical and clinical data are now available that do not indicate this. Dr. Sheybani agreed with Dr. Chen.

What are the roles of FUS with novel therapeutic vectors (lipid nanoparticles, mRNA, CRISPR, etc.): improved delivery, targeted delivery?

Dr. Todd: Wide-ranging dosing characterizes all of this work. But before we standardize dosage, we need collaboration among groups to collect knowledge from other fields to define new directions. Then we need to demonstrate that FUS can achieve that goal.

Outside of brain indications, what additional indications should be pursued with FUS in combination with gene and cell therapies?

Dr. Aubert: AAV is easiest for translational medicine, but it can only be done once. Since that obviates repeating the treatment, combining therapies may be an answer.

Dr. Sheybani: For the rare disease that affects the brain, to determine whether the disease spreads to the whole brain, you look at biodistribution, particularly in the CNS. The degree of biodistribution you want depends on the etiology of the disease. This relates to broad vs. focused distribution and implies the use of combined therapies. Dr. Chen agreed with Dr. Sheybani.

.

Left to right

Bob Smith

Russell Cruz, MD, PhD

Natasha Sheybani, PhD

Hong Chen, PhD

Nick Todd, PhD



Closing Remarks

Neal Kassell

Focused Ultrasound Foundation

Dr. Kassell thanked the more than 400 in-person and 200 virtual participants, and the sponsors that make the meeting possible, for an outstanding symposium. The symposium's three objectives—to share ideas and information as a way of creating knowledge, to create new relationships and strengthen existing relationships to foster collaboration and innovation, and to have fun—were all accomplished.

He solicited feedback on the hybrid format of the symposium and whether to continue holding a symposium specific to FUS when it has now made its way into most specialty meetings. The FUS symposium was created in 2008, when there were few forums for the community to present its work and when the current video conferencing and virtual presentation capabilities did not exist. With the marked change in the environment, it may be time for the Foundation to reimagine the symposium and continue to follow its path of creative destruction. Because the Foundation and the FUS community have been successful in increasing awareness of FUS, this has created a proliferation and abundance of opportunities to present material at other meetings, including IEEE, the American Institute of Ultrasound in Medicine, the Radiological Society of North America, and the International Society for Therapeutic Ultrasound. There are many opportunities that did not exist in the past.

Going forward, the Foundation plans to markedly increase the number of workshops and roundtables it sponsors. In fact, workshops on gene therapy, sonodynamic therapy for GBM, veterinary indications, Alzheimer's disease, and more are already being planned.

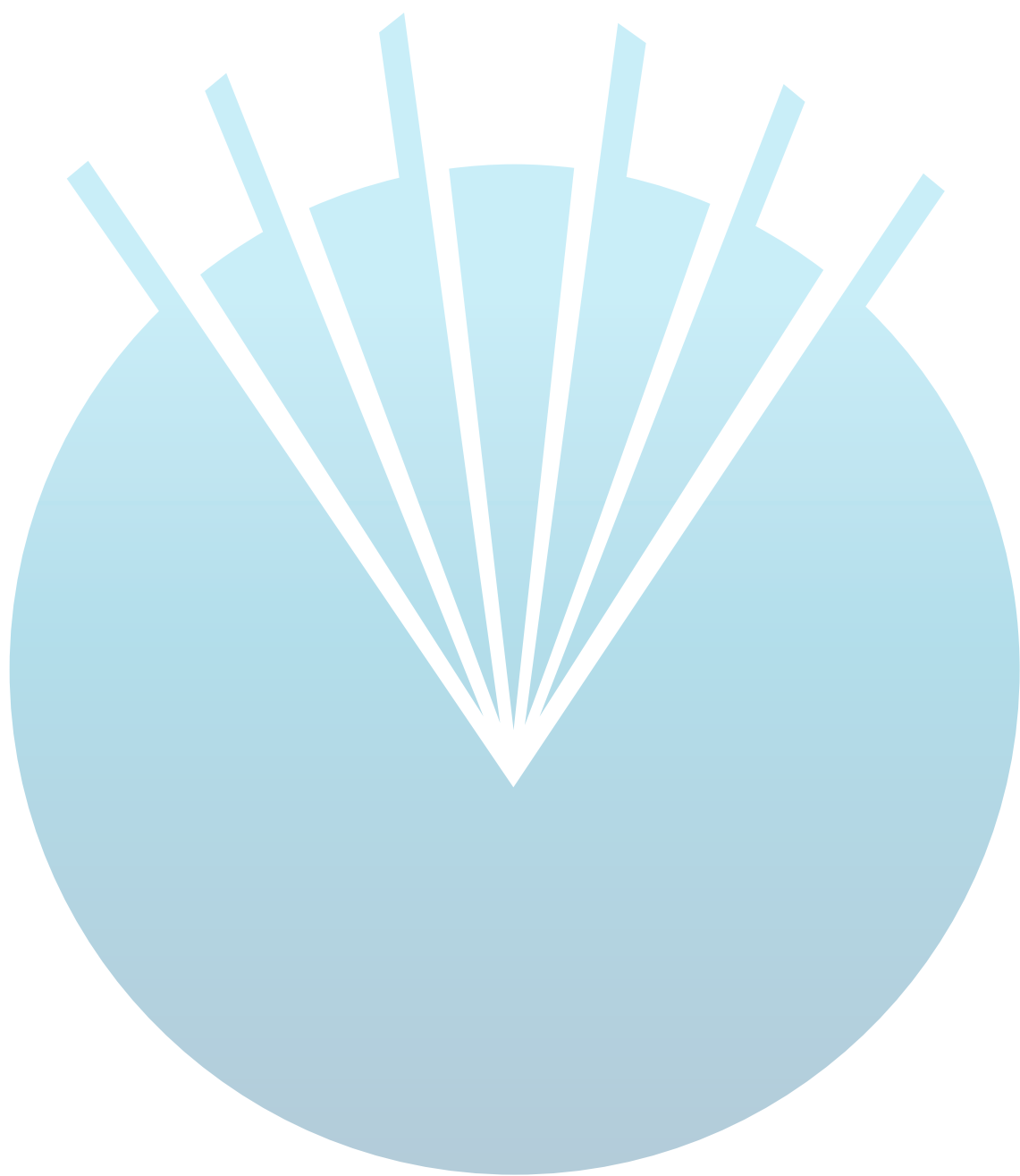
Dr. Kassell said that he was encouraged by the number of young people in the field. The Foundation will create more opportunities for young people to attend meetings and will increase the number of internships and fellowships that it sponsors.

He closed by again thanking all attendees for an incredibly rewarding symposium experience, and he thanked Foundation staff members for making the symposium what it is today.

.....



View on the Foundation's
[YouTube channel](#) >





FOCUSED
ULTRASOUND
FOUNDATION

1230 Cedars Court, Suite 206
Charlottesville, VA 22903, USA

+1 434.220.4993
fusfoundation.org