

Focused Ultrasound *for Epilepsy*

Overview

Focused ultrasound is an early stage, noninvasive therapeutic technology with the potential to improve the quality of life and decrease the cost of care for patients with epilepsy. This novel technology precisely focuses beams of ultrasound energy on targets deep within the brain without damaging surrounding normal tissue. Where the beams converge, the ultrasound can produce a variety of therapeutic effects on brain tissue, enabling the incisionless treatment of epilepsy.

Benefits

Current treatments for epilepsy include medication, surgery, radiofrequency or laser ablation, deep brain stimulation, and stereotactic radiosurgery, all of which have limitations and side effects. Focused ultrasound has the potential to provide an alternative to invasive surgery or to replace radiosurgery for treatment of medication refractory epilepsy.

Advantages:

- **Noninvasive** - no incisions, no risk of infection or bleeding, less pain, and rapid recovery
- **Image-guided** - precision targeting with minimal damage to surrounding tissue
- **Real time target confirmation** - using sub-ablative treatment parameters, the target can be tested for location accuracy prior to ablation
- **Safe, temporary and repetitive opening of the blood brain barrier (BBB)** - enhancing the delivery of therapeutics directly to the brain target site
- **Fractionated ablation** - ability to treat in a step-wise fashion in order to preserve tissue
- **No ionizing radiation** - fewer side effects and can be safely repeated
- **Conformal** - treatment confined within the boundaries of the entire targeted volume

State of the Field

Clinical and preclinical trials are evaluating various applications of focused ultrasound to treat epilepsy.

Clinical trials at University of Virginia and Nicklaus Children's Hospital in Miami Florida are using focused ultrasound to induce thermal ablation at specific regions within the brain where certain types of seizures originate. The targeted regions include tumors or abnormally functioning tissues located deep in the brain or abnormal brain tissue located in the subcortical regions near the surface of the brain.

At The Ohio State University, the goal is to stop the propagation of the seizures by ablating the anterior thalamic nucleus, a critical node involved in the generalization of seizures.

At Brigham and Women's Hospital, UCLA, and Taipei Veteran's General Hospital, clinical trials are underway to investigate another mechanism of action for focused ultrasound – neuromodulation – in the treatment of medication refractory epilepsy. In these studies, lower energy pulsed ultrasound is applied to epileptogenic foci within the brain to alter the transmission of neuronal pathways that lead to seizures.

Preclinical laboratory studies continue to research various methods of how focused ultrasound could treat epilepsy. Mechanisms that researchers are exploring in this preclinical space include opening the blood brain barrier (BBB) to enhance the delivery of therapeutics to the affected area, mechanical ablation (histotripsy) of the diseased tissue, and optimization of focused ultrasound parameters for neuromodulation and thermal ablation.

For more information visit www.fusfoundation.org/diseases-and-conditions/neurological/epilepsy

Focused Ultrasound Foundation

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Mechanisms of Action

Focused ultrasound delivers a variety of effects on tissue, and the following mechanisms are currently in use or under investigation for the treatment of epilepsy.

TISSUE DESTRUCTION

- **Thermal Ablation:** coagulative cell death
- **Histotripsy:** mechanical cell disruption

DELIVERY OF THERAPEUTIC AGENTS

- **BBB opening:** increased diffusion of therapeutics to targeted brain tissue

NEUROMODULATION

- Alteration of neuronal activity through targeted delivery of a focused ultrasound stimulus

For a complete list of focused ultrasound's mechanisms of action, see the Foundation's website: www.fusfoundation.org/the-technology/mechanisms-of-action

Research Project Inventory

Clinical Trials

- * MR-Guided Focused Ultrasound in the Treatment of Subcortical Lesional Epilepsy (University of Virginia – Charlottesville, Virginia, United States)
- Low Intensity Focused Ultrasound Treatment for Drug-Resistant Epilepsy: An Efficacy Trial (Brigham and Women's Hospital – Boston, Massachusetts, United States)
- * A Pilot Study: Focused Ultrasound Thalamotomy for the Prevention of Secondary Generalization in Focal Onset Epilepsy (The Ohio State University – Columbus, Ohio, United States)
- Low-intensity Focused Ultrasound Pulsation (LIFUP) for Treatment of Temporal Lobe Epilepsy (UCLA – Los Angeles, California, United States)
- Safety of Using NaviFUS System in Patients with Drug Resistant Epilepsy (Taipei Veterans General Hospital – Taipei, Taiwan)
- * A Feasibility Safety Study Using the ExAblate 4000 system in Management of Benign Centrally-Located Intracranial Tumors Which Require Clinical Intervention in Pediatric and Young Adult Subjects (Nicklaus Children's Hospital – Miami, Florida, United States)

Preclinical Laboratory Studies

- * Use of low-intensity focused ultrasound for the non-invasive, focal disconnection of brain circuitry in the treatment of neurological disorders (University of Virginia – Charlottesville, Virginia, United States)
- Investigating the Feasibility of Targeting Temporal Lobe using Transcranial MRI- Guided Focused Ultrasound (University of Maryland – Baltimore, Maryland, United States)
- MRI of Skull Heating During Focused Ultrasound Neurosurgery (University of Virginia – Charlottesville, Virginia, United States)
- * The Focused Ultrasound Foundation is fully or partially funding these research projects.

Research Sites

Clinical Trials

Brigham and Women's Hospital (Boston, MA, United States)
Nicklaus Children's Hospital (Miami, FL, United States)
Ohio State University (Columbus, OH, United States)
Taipei Veterans General Hospital (Taipei City, Taiwan)
University of California Los Angeles (Los Angeles, CA, United States)
University of Virginia Health System (Charlottesville, VA, United States)

Preclinical Laboratory Studies

Brigham and Women's Hospital (Boston, MA, United States)
Children's National Health System (Washington, DC, United States)
Hôpitaux Universitaires Pitié-Salpêtrière (Paris, France)
Hospital for Sick Children (Washington, DC, United States)
Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (Shenzhen, China)
Stanford University School of Medicine (Stanford, CA, United States)
Sunnybrook Health Sciences Centre (Toronto, ON, Canada)
University of Maryland School of Medicine (Baltimore, MD, United States)
University of Virginia Health System (Charlottesville, VA, United States)
Virginia Polytechnic Institute and State University (Blacksburg, VA, United States)

Manufacturers

BrainSonix Corp. | Sherman Oaks, CA | www.brainsonix.com

INSIGHTEC LTD | Tirat Carmel, Israel | www.insightec.com

NaviFUS | New Taipei City, Taiwan | www.navi-fus.com

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Media

[Ohio State Leading First-in-World Study using Focused Ultrasound to Treat Epilepsy](#)

Wexner Medical Center Press Release - January 28, 2019

“We’re pursuing this clinical trial because there’s a large unmet clinical need. More than 20 million people worldwide live with uncontrollable seizures because no available treatment works for them.” - Dr. Vibhor Krishna, Lead Principal Investigator and Neurosurgeon at The Ohio State University Wexner Medical Center

[Focused ultrasound offers potential new epilepsy treatment](#)

Physics World - January 29, 2019

“This is an important step in the evolution of focused ultrasound as a mainstream therapy for disorders affecting the brain. Ultimately, the results of this study could lead to new, more effective therapies for certain patients with epilepsy.” - Dr. Neal Kassell, founder and chairman of the Focused Ultrasound Foundation.

[Ultrasound-activated nanoparticles provide targeted control of brain activity](#)

Physics World - December 10, 2018

“The first trial we’re looking to do is to localize epileptogenic regions in the brain of patients with treatment resistant epilepsy who are slated for neurosurgery, to validate that the intended surgical volume is indeed the generator of abnormal brain activity - and to ensure that removing it wouldn’t induce an unexpected functional deficit like aphasia or amnesia.” - Dr. Raag Airan, Assistant Professor of Neuroradiology, Stanford University School of Medicine.

[UVA leading use of focused ultrasound for rare brain masses](#)

The Daily Progress - June 3, 2018

“We wouldn’t normally recommend surgery for hypothalamic hamartomas unless it was severe and causing other problems. So, to have something minimally invasive is really ideal.” - Dr. Nathan Fountain, director of UVA School of Medicine Epilepsy Program

Key Publications

- Brinker ST, Preiswerk F, White PJ, Mariano TY, McDannold NJ, Bublick EJ. Focused Ultrasound Platform for Investigating Therapeutic Neuromodulation Across the Human Hippocampus. *Ultrasound Med Biol.* 2020;46(5):1270-1274. doi:10.1016/j.ultrasmedbio.2020.01.007
- Lin Z, Meng L, Zou J, Zhou W, et al. Non-invasive ultrasonic neuromodulation of neuronal excitability for treatment of epilepsy. *Theranostics* 2020;10(12):5514-5526.doi:10.7150/thno.40520
- Abe K, Yamaguchi T, Hori H, et al. Magnetic resonance-guided focused ultrasound for mesial temporal lobe epilepsy: a case report. *BMC Neurology* 2020;20:160. doi:10.1186/s12883-020-01744-x
- Zhang Y, Zhou H, Qu H, et al. Effects of Non-invasive, Targeted, Neuronal Lesions on Seizures in a Mouse Model of Temporal Lobe Epilepsy. *Ultrasound Med Biol.* February 2020. doi:10.1016/j.ultrasmedbio.2020.01.008
- Ranjan M, Boutet A, Bhatia S, et al. Neuromodulation beyond neurostimulation for epilepsy: scope for focused ultrasound. *Expert Rev Neurother.* July 2019:1-7. doi:10.1080/14737175.2019.1635013
- Chen S-G, Tsai C-H, Lin C-J, et al. Transcranial focused ultrasound pulsation suppresses pentylentetrazol induced epilepsy in vivo. *Brain Stimul.* September 2019. doi:10.1016/j.brs.2019.09.011
- Monteith S, Snell J, Eames M, Kassell NF, Kelly E, Gwinn R. Transcranial magnetic resonance-guided focused ultrasound for temporal lobe epilepsy: a laboratory feasibility study. *J Neurosurg.* 2016;125(6):1557-1564. doi:10.3171/2015.10.JNS1542
- Zhang Y, Tan H, Bertram EH, et al. Non-Invasive, Focal Disconnection of Brain Circuitry Using Magnetic Resonance-Guided Low-Intensity Focused Ultrasound to Deliver a Neurotoxin. *Ultrasound Med Biol.* 2016;42(9):2261-2269. doi:10.1016/j.ultrasmedbio.2016.04.019
- Hakimova H, Kim S, Chu K, Lee SK, Jeong B, Jeon D. Ultrasound stimulation inhibits recurrent seizures and improves behavioral outcome in an experimental model of mesial temporal lobe epilepsy. *Epilepsy Behav.* 2015;49:26-32. doi:10.1016/j.yebeh.2015.04.008
- Quigg M, Harden C. Minimally invasive techniques for epilepsy surgery: stereotactic radiosurgery and other technologies. *J Neurosurg.* 2014;121 Suppl:232-240. doi:10.3171/2014.8.GKS141608
- Min B-K, Bystritsky A, Jung K-I, et al. Focused ultrasound-mediated suppression of chemically-induced acute epileptic EEG activity. *BMC Neurosci.* 2011;12(1):23. doi:10.1186/1471-2202-12-23