Overview

Focused ultrasound is an early-stage, non-invasive, therapeutic technology with the potential to improve the quality of life and decrease the cost of care for patients with Alzheimer’s disease. This novel technology precisely focuses beams of ultrasonic energy on targets deep in the brain without damaging surrounding normal tissue. Where the beams converge, the ultrasound can produce a variety of therapeutic effects without incisions or radiation. For Alzheimer’s disease, the ultrasound beam opens the blood-brain barrier (BBB), a naturally occurring barrier of tightly aligned cells along blood vessels that inhibits the diffusion of medications and immune cells into the brain.

Benefits

Currently, there is no cure or effective treatment for Alzheimer’s disease. Potentially promising drug and antibody therapies have proven ineffective due to their inability to cross the BBB and enter the brain.

Advantages:
- Noninvasive – no surgery
- Precision targeting – treatment to affected areas – minimize damage to healthy tissue
- Opens BBB safely – enhanced drug delivery and immune effects

State of the Field

The first in-human pilot study for focused ultrasound in patients with Alzheimer’s disease completed enrollment and results were presented at the Alzheimer’s Association International Conference and published in *Nature Communications* in 2018. The Focused Ultrasound Foundation convened the scientific and medical community through workshops and steering committees to create and fund this project. Further clinical trials are now underway at four institutions to determine if different and larger areas of the brain in patients with Alzheimer’s disease can be opened repetitively and safely with focused ultrasound.

Recent preclinical studies at various laboratories have independently reported the ability of focused ultrasound to safely open the BBB, which decreased amyloid plaque burden and improved memory in mice models with Alzheimer’s disease. Additional animal studies reported enhanced delivery of anti-amyloid and tau antibodies to the brain with focused ultrasound, reducing the number of plaques and improving cognition. Further focused ultrasound research is investigating the possibility of delivering even higher concentrations of disease modifying drugs into the brain. Other preclinical work involves whole brain focused ultrasound, which has shown to increase blood vessel formation and nerve cell regeneration in Alzheimer’s disease mice models.

For more information visit www.fusfoundation.org/diseases-and-conditions/neurological/alzheimers-disease
Mechanisms of Action

**Blood-Brain Barrier (BBB) Opening** – Focused ultrasound can reversibly and safely allow the blood vessels in the brain to partially “open” the otherwise tight junctions, allowing certain medications, therapies, and the patient’s own immune cells to diffuse into the diseased brain tissue.

**Targeted Drug Delivery (TDD)** – An encapsulated therapy (genes, antibodies, medications) circulates harmlessly throughout the body until it is released and activated by the focused ultrasound beam through either elevated temperatures or pressures in the targeted, diseased area.

**Immunomodulation** – Focused ultrasound may “awaken” the immune system, allowing the patient’s body to help eliminate the amyloid plaques and tau proteins that accumulate in Alzheimer’s disease.

**Stem Cell Homing** – The mechanical effects of focused ultrasound can stimulate the release of chemoattractant molecules and increase the expression of cellular adhesion molecules on endothelial cells, both of which improve the ability of stem cells to promote neuronal regeneration.

Research Project Inventory

**Technical**

* Neuronavigation-guided and Ultrasound Monitored Human BBB opening FUS Prototype System (Elisa Konofagou, PhD - Columbia University)

**Preclinical Studies**

* Effects of FUS on CNS Uptake and Efficacy of an Anti-Amyloid Antibody in Aged AD Transgenic Mice-Cohort -2 (Cynthia Lemere, PhD - Brigham and Women’s Hospital)
* Effects of FUS on CNS Uptake and Efficacy of an Anti-Amyloid Antibody in Aged AD Transgenic Mice (Cynthia Lemere, PhD - Brigham and Women’s Hospital)
* BBB Opening for facilitating drug delivery in neurological and neurodegenerative diseases in nonhuman primates (Elisa Konofagou, PhD - Columbia University)

**Clinical Trials**

* Blood-Brain Barrier Opening Using Focused Ultrasound with IV US Contrast Agents in Patients with Early Alzheimer’s Disease (Nir Lipsman, MD, PhD - Sunnybrook)
* A Phase IIa Study to Evaluate the Safety and Efficacy of Blood-Brain Barrier (BBB) Opening Using Transcranial MR-Guided Focused Ultrasound in Patients With Alzheimer’s Disease (Nir Lipsman, MD, PhD - Sunnybrook)

Assessment of Safety and Efficacy of ExAblate Blood-Brain Barrier Disruption for the Treatment of Patients With Probable Alzheimer’s Disease (Weill Cornell, Ohio State, West Virginia)

Study of Non-Invasive Deep Brain Stimulation With Low Intensity Focused Ultrasound Pulse (LIFUP) for Mild Cognitive Impairment (MCI) and Mild Alzheimer’s Disease (Gary Small, MD - UCLA)

Phase 1/2 Open Single-arm Monocentric Study Evaluating the Tolerance and Interest of Transient Opening of the Blood-Brain Barrier by Low Intensity Pulsed Ultrasound With the SONOCLOUD® Implantable Medical Device in Mild Alzheimer’s Disease Patients (Stephane Epelbaum, MD, PhD - Hopitaux de Paris)

Pilot Study of Focused Ultrasound Stimulator System (NS-US100) to Evaluate Efficacy and Safety of BBB (Blood-Brain Barrier) Disruption for Alzheimer’s Disease Patients (Catholic University of Korea)

* The Focused Ultrasound Foundation is fully or partially funding these research projects.
Focused Ultrasound for Alzheimer’s Disease

Research Sites

Preclinical*
- BrainSonix Corp. (United States)
- CarThera, SA. (France)
- Catholic University of Korea
- Columbia University
- Commissariat à l'énergie atomique et aux énergies alternatives (France)
- Cyprus University of Technology
- Hôpitaux Universitaires Pitié-Salpêtrière (France)
- Johns Hopkins University School of Medicine
- Ohio State University
- Rostov Scientific Research Institute of Oncology (Russia)
- Sunnybrook Health Sciences Centre (Canada)
- TheraWave, LLC. (United States)
- Universidad de Puerto Rico
- Universität Heidelberg
- Universitäts-Kinderklinik Zürich, FUS-Center
- University of Calgary Hospital
- University of Dundee, Institute for Medical Science and Technology (United Kingdom)
- University of Queensland
- University of Texas Southwestern Medical Center
- University of Virginia Health System
- US Food and Drug Administration

Clinical
- Catholic University of Korea
- Hôpitaux Universitaires Pitié-Salpêtrière (France)
- Ohio State University
- Queensland Brain Institute (Australia)
- Sunnybrook Health Sciences Centre (Canada)
- University of California, Los Angeles
- Weill Cornell Medical Center (United States)
- West Virginia University, Robert C. Byrd Health Sciences Center

* More than 200 preclinical laboratory sites are investigating focused ultrasound to treat neurological diseases.

Manufacturers

CarThera | Paris, France, www.carthera.eu
INSIGHTEC LTD | Tirat Carmel, Israel, www.insightec.com
MBInsight Systems | Miaoli County, Taiwan
NaviFUS | New Taipei City, Taiwan, www.navi-fus.com
TheraWave, LLC | New York, NY
Focused Ultrasound for Alzheimer’s Disease

Media

Dementia symptoms reversed in mice, human trials next after federal funding announced
ABC News Australia – December 17, 2018

“Cognition was restored. So the mice were perfectly fine afterwards, which was a surprise to us, but obviously was extremely encouraging.” – Dr. Jürgen Götz, Queensland Brain Institute, University of Queensland

Battling Alzheimer’s through Better Access to the Brain
Scientific American – November 2, 2018

“A growing body of studies is showing that MRgFUS can be a safe, reversible, and noninvasive method to open the blood-brain barrier.” – Dr. Ali Rezai, Director of the Rockefeller Neuroscience Institute at West Virginia University

Ultrasound Jiggles Open Brain Barrier, a Step to Better Care
US News & World Report – July 25, 2018

“It’s been a major goal of neuroscience for decades, this idea of a safe and reversible and precise way of breaching the blood-brain barrier...it’s exciting.” – Dr. Nir Lipsman, Sunnybrook Health Sciences Centre

“It’s definitely promising...What is remarkable is that they could do it in a very focused way, they can target a very specific brain region.” – Dr. Eliezer Masliah, National Institute on Aging

The Second Coming of Ultrasound
WIRED – January 22, 2018

“We’re starting to realize they (microbubbles) can be much more versatile. We can chemically design their shells to alter their physical properties, load them with tissue-seeking markers, even attach drugs to them.” – Dr. Tao Sun, Postdoctoral Research Fellow at the Brigham and Women’s Hospital and Harvard Medical School

Getting Drugs Past the Blood-Brain Barrier
The Scientist – November 1, 2017

“We worked on this for 15 years doing animal studies, and we’re at the point where it’s ready to go to the clinic.” – Dr. Nathan McDannold, Brigham and Women’s Hospital
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Videos

Associated Press: Ultrasound Jiggles Open Brain Barrier

Rick Karr: Alzheimer’s Patient, Sunnybrook Health Sciences Centre

Dr. Nir Lipsman: Explains the effects of focused ultrasound on blood-brain barrier opening

To view these and other videos about focused ultrasound technology and patients, visit https://www.fusfoundation.org/the-foundation/news-media/multimedia
Focusing Ultrasound for Alzheimer’s Disease

Key Publications


Focused Ultrasound for Alzheimer’s Disease

Key Publications


