

Focused Ultrasound *for Alzheimer's Disease*

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 ultrasound 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, focused ultrasound opens the blood-brain barrier (BBB), a naturally occurring barrier of tightly aligned cells along blood vessels that normally 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 incisions, no risk of infection or bleeding, less pain, and rapid recovery
- **Image-guided** - minimal damage to surrounding tissue
- **Safe, temporary and repetitive opening of the blood brain barrier (BBB)** - enhancing the delivery of therapeutics and immune cells directly to the brain target site

State of the Field

The first Phase I Clinical Trial using focused ultrasound to open the BBB in patients with Alzheimer's disease was completed at Sunnybrook Hospital, and results are published. This initial study reported safe, repeated and reversible opening of the blood brain barrier without clinical or radiographic adverse events. There is now a Phase II Clinical Trial taking place at Sunnybrook to establish the clinical effect of repetitive BBB opening in patients with Alzheimer's disease. Along with this Phase II trial, there are three additional ongoing clinical trials that are examining the effect of focused ultrasound mediated BBB opening at various target locations in patients with Alzheimer's disease.

Multiple recent preclinical laboratory studies have reported decreases in amyloid plaque burden and improved memory after focused ultrasound-induced BBB opening in animal subjects. Additional preclinical 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 demonstrated increased neurogenesis and improved cognition after BBB opening in an animal dementia model. Other preclinical work involves whole brain focused ultrasound, which has been shown to increase blood vessel formation and nerve cell regeneration in Alzheimer's disease mouse models.

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

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 Alzheimer's disease.

DELIVERY OF THERAPEUTIC AGENTS

- **BBB opening:** increased diffusion of therapeutics and immune cells to targeted brain tissue
- **Carrier mediated vehicle:** locally activate encapsulated therapies
- **Sonoporation:** temporarily create pores in the cell membrane, enhancing the delivery of therapeutics into cells
- **Stem cell homing:** migration of stem cells to target area, promoting regeneration of tissue

IMMUNOMODULATION

- **Enhanced delivery and activation of immune cells**

For a complete list of all 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

- * 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 (Sunnybrook Health Sciences Centre)
- *Assessment of Safety and Efficacy of ExAblate Blood-Brain Barrier Disruption for the Treatment of Patients with Probable Alzheimer's Disease (Yonsei University College of Medicine)
- Exablate Blood-Brain Barrier (BBB) Disruption for the Treatment of Alzheimer's Disease (Weill Cornell University, West Virginia University)
- *Non-invasive Blood-brain Barrier Opening in Alzheimer's Disease Patients Using Focused Ultrasound (Columbia University)
- Deep Brain Stimulation with LIFUP for Mild Cognitive Impairment and Mild Alzheimer's Disease (UCLA Semel Institute)

Preclinical Laboratory Studies

- *Effects of FUS on CNS Uptake and Efficacy of an Anti-Amyloid Antibody in Aged Alzheimer's Transgenic Mice (Brigham and Women's Hospital)
- *Blood-brain barrier opening for facilitating drug delivery in neurological and neurodegenerative diseases in non-human primates (Columbia University)
- *Enhancing Neurogenesis by Focused Ultrasound-mediated Plasmid Delivery (University of Virginia)

*The Focused Ultrasound foundation is partially or fully funding these studies.

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Research Sites

Clinical Trials

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

Preclinical Laboratories

Brigham and Women's Hospital (United States)
Columbia University (United States)
Commissariat à l'énergie atomique et aux énergies alternatives (France)
Cyprus University of Technology (Cyprus)
Hôpitaux Universitaires Pitié-Salpêtrière (France)
Ohio State University (United States)
Rostov Scientific Research Institute of Oncology Russian Federation (Russia)
Sunnybrook Health Sciences Centre (Canada)
Universität Heidelberg (Germany)
University of Calgary Hospital (Canada)
University of Dundee, Institute for Medical Science and Technology (United Kingdom)
University of Queensland (Australia)
University of Texas Southwestern Medical Center (United States)
University of Virginia (United States)
US Food and Drug Administration (United States)

Manufacturers

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

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

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Media

[Blood-brain barrier's opening increases Alzheimer's treatment's efficacy](#)

Korean Biomed - November 20, 2021

"By allowing treatments to safely cross the BBB, which has been a major obstacle in using therapeutics, the team expects that the research will provide an opportunity to find a breakthrough treatment for dementia." - Ye Byoung-seok, Department of Neurology, Severance Hospital in Seoul Korea

[Investigating the Use of MR-Guided Focused Ultrasound in Alzheimer's Disease](#)

Neurology Live - November 17, 2021

"This current study was a continuation of the safety and efficacy clinical trial. The objective was to look at what happens long-term when we open the blood-brain barrier in the hippocampus, the frontal lobes, and the parietal lobes of individuals with mild Alzheimer's disease." - Dr. Ali Rezai, West Virginia University

[Metal-based molecules show promise against the build-up of Alzheimer's peptides](#)

Imperial College London - July 13, 2021

"The molecule we have designed is able to interfere with amyloid and seems non-toxic, and it can be delivered across the blood brain barrier using ultrasound, which means you don't need an invasive procedure." - Tiffany Chan, Department of Chemistry and Bioengineering, Imperial College London

[Stepping Up to Beat Alzheimer's - Meet Judi Polak, Alzheimer's patient and star of a clinical trial showing promising results](#)

AARP - December 11, 2019

"One of our good friends said that the first person to [one day] be cured with Alzheimer's is alive today. That became our mantra and fight song. I choose not to suffer, not to die, but to fight." - Judi Polak, Alzheimer's patient and first to receive Focused Ultrasound for BBB opening in a clinical trial.

[Can ultrasound be used to fight Alzheimer's?](#)

PBS NewsHour - October 11, 2019

At age 61, Judi Polak is five years into a bleak diagnosis: Alzheimer's disease. But last year she made medical history in a clinical trial, when a team of scientists, engineers and practitioners deployed a novel device to take aim at a big barrier in the fight against her illness.

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Key Publications

- Götz J, Richter-Stretton G, Cruz E. Therapeutic Ultrasound as a Treatment Modality for Physiological and Pathological Ageing Including Alzheimer's Disease. *Pharmaceutics*. 2021 Jul 1;13(7):1002.
- Park SH, Baik K, Jeon S, Chang WS, Ye BS, Chang JW. Extensive frontal focused ultrasound mediated blood-brain barrier opening for the treatment of Alzheimer's disease: a proof-of-concept study. *Transl Neurodegener*. 2021 Nov 5;10(1):44.
- Chan TG, Ruehl CL, Morse SV, Simon M, Rakers V, Watts H, Aprile FA, Choi JJ, Vilar R. Modulation of amyloid- β aggregation by metal complexes with a dual binding mode and their delivery across the blood-brain barrier using focused ultrasound. *Chem Sci*. 2021 Jun 15;12(27):9485-9493.
- Sun T, Shi Q, Zhang Y, Power C, Hoesch C, Antonelli S, Schroeder MK, Caldarone BJ, Taudte N, Schenk M, Hettmann T, Schilling S, McDannold NJ, Lemere CA. Focused ultrasound with anti-pGlu3 A β enhances efficacy in Alzheimer's disease-like mice via recruitment of peripheral immune cells. *J Control Release*. 2021 Aug 10;336:443-456.
- Mathew AS, Gorick CM, Price RJ. Multiple regression analysis of a comprehensive transcriptomic data assembly elucidates mechanically- and biochemically-driven responses to focused ultrasound blood-brain barrier disruption. *Theranostics*. 2021 Oct 11;11(20):9847-9858.
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- D'Haese PF, Ranjan M, Song A, Haut MW, Carpenter J, Dieb G, Najib U, Wang P, Mehta RI, Chazen JL, Hodder S, Claassen D, Kaplitt M, Rezai AR. β -Amyloid Plaque Reduction in the Hippocampus After Focused Ultrasound-Induced Blood-Brain Barrier Opening in Alzheimer's Disease. *Front Hum Neurosci*. 2020 Oct 7;14:593672.
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Key Publications

- Janowicz PW, Leinenga G, Götz J, Nisbet RM. Ultrasound-mediated blood-brain barrier opening enhances delivery of therapeutically relevant formats of a tau-specific antibody. *Sci Rep*. 2019 Jun 25;9(1):9255.
- Nicodemus NE, Becerra S, Kuhn TP, Packham HR, Duncan J, Mahdavi K, et al. Focused transcranial ultrasound for treatment of neurodegenerative dementia. *Alzheimers Dement N Y N*. 2019;5:374-81.
- Weber-Adrian D, Kofoed RH, Chan JWY, Silburt J, Noroozian Z, Kügler S, et al. Strategy to enhance transgene expression in proximity of amyloid plaques in a mouse model of Alzheimer's disease. *Theranostics*. 2019;9(26):8127-37.
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