FOCUSED ULTRASOUND FOUNDATION

Focused Ultrasound *for Parkinson's Disease*

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 Parkinson's disease (PD). 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 enabling the treatment of PD without incisions or radiation.

Benefits

Currently, there is no cure for Parkinson's and the major options for treatment include drug therapy and invasive surgery (e.g. deep brain stimulation, radiofrequency lesioning).

Focused ultrasound has the ability to noninvasively treat some PD patients through precise thermal ablation of the tracts that cause motor symptoms. Focused ultrasound can also open the blood-brain barrier (BBB), a naturally occurring barrier of tightly aligned cells along the blood vessels that inhibits the diffusion of medications into the brain that can potentially prevent progression and/or restore function. Benefits compared to current treatments:

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

State of the Field

In December 2018, the FDA approved the use of focused ultrasound for treating patients with tremor dominant Parkinson's.

Clinical trials are now underway to evaluate if additional symptoms from PD, such as dyskinesia and involuntary movements, can be treated with focused ultrasound. These studies are also attacking the disease at various target locations within the brain. So far, these procedures have safely treated one side of the brain in PD patients and projects will soon assess the ability to treat both sides with staged treatments.

Recent preclinical laboratory studies demonstrate focused ultrasound's ability to safely and temporarily open the BBB, improving the delivery of various neurotherapeutics, including:

- Genes, growth factors, stem cells, neuroprotective and/or neurorestorative drugs
- Anti-alpha synuclein antibodies

These various substances have the ability to slow the progression of the disease, halt neurodegeneration, and even promote healthy neuronal regeneration. Increasing dopamine levels and dopaminergic neuron density was reported to restore function in PD animal models with no local or systemic toxicity.

An early pilot study is also evaluating the safety and feasibility of opening the BBB in patients with Parkinson's dementia in hopes that if successful, disease modifying drugs can be delivered to the brain.

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

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Mechanisms of Action

Thermal ablation - Focused ultrasound can elevate temperatures in a targeted region producing coagulative cell death.

Sonoporation - The non-thermal effects of focused ultrasound can temporarily create pores in the cell membrane, allowing therapeutics to enter the interior of the cell and exert maximum efficacy.

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

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

Neuromodulation – Focused ultrasound can stimulate underactive neural activity or inhibit overactive neural activity in precise regions in the brain.

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.

Immunomodulation – Focused ultrasound may "awaken" the immune system, potentially enabling the patient's own body to help eliminate the alpha-synuclein protein that accumulates in Parkinson's disease.

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Research Project Inventory

Preclinical Studies

* MRgFUS Blood-Brain Barrier Drug Delivery with AAV2 Gene Therapy Microbubble Drug Conjugates (James Keenan, MS - Artenga, Inc)

* MRgFUS Gene Delivery for Neuroprotection in Parkinson's Disease (Michael Kaplitt, MD, PhD - Cornell)

* Antibody Delivery Through the BBB Opening in an Alpha-Synuclein Model (Elisa Konofagou, PhD - Columbia)

* Minimally-Invasive Therapy for Parkinson's Disease Achieved by the Focused Ultrasound-Targeted Delivery of Gene-Bearing Nanocarriers (Justin Hanes, PhD - Johns Hopkins)

* Focused Ultrasound for Increased Delivery of Intranasal DNA Nanoparticles to Rat Brain (Barbara Waszczak, PhD - Northeastern University)

Clinical Trials

* A Feasibility Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms of Advanced Idiopathic Parkinson's Disease With Unilateral Lesioning of the Globus Pallidum Using the ExAblate Transcranial System (Stanford University, University of Maryland, Brigham and Women's Hospital, Ohio State Wexner Medical Center, University of Virginia)

* Management of the Medically-Refractory Motor Symptoms of Advanced Idiopathic Parkinson's Disease With Unilateral Lesioning of the Subthalamic Nucleus Using the ExAblate Transcranial System (University of Virginia)

Feasibility Trial Evaluating the Safety and Efficacy of ExAblate Transcranial Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for Unilateral Pallidotomy for the Treatment of L-Dopa Induced Dyskinesia (LID) of Parkinson's Disease (Michael Schwartz, MD - Sunnybrook)

A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease With Unilateral Lesioning of the Globus Pallidum Using the ExAblate Neuro System (Stanford University, University of Maryland, Brigham and Women's Hospital, Ohio State Wexner Medical Center, University of Virginia, Mayo Clinic, Pennsylvania Hospital, Swedish Medical Center, Toronto Western, Rambam Medical Center, Severance, St. Mary's Hospital)

A Study to Evaluate the Safety and Feasibility of Temporary Blood Brain Barrier Disruption (BBBD) Using ExAblate MR Guided Focused Ultrasound in Patients With Parkinson's Disease Dementia (Jose Obeso, MD, PhD - Centro Integral de Neurociencias HM Cinac)

* The Focused Ultrasound Foundation is fully or partially funding these research projects.

Focused Ultrasound *for Parkinson's Disease*

Research Project Inventory

Clinical Trials (Cont.)

A Feasibility Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MR Guided Focused Ultrasound for Unilateral Pallidotomy in the Treatment of Dyskinesia of Parkinson's Disease (JW Chang, MD - Yonsei University Health System)

ExAblate Transcranial MR Guided Focused Ultrasound for the Treatment of Parkinson's Disease Exablate Transcranial MRgFUS targeting the Pallidothalamic Tracts for PD- a Staged Bilateral Approach (Takaomi Taira, MD - Tokyo Women's Hospital)

* A Prospective, Randomized, Sham Controlled Study to Evaluate the Safety and Efficacy of ExAblate Subthalomotomy for the Treatment of Parkinson's Disease Motor Features (Jose Obeso, MD, PhD - Centro Integral de Neurociencias HM Cinac)

* Functional Neuroimaging Feedback for Focused Ultrasound Thalamotomy for Tremor Surgery (Vibhor Krishna, MD, MBBS - Ohio State University)

The Effect of Lesion Characteristics in Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS) on Tremor in Essential Tremor and Parkinson's Disease (Menashe Zaaroor, MD - Rambam Medical Center)

A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders (Michael Schwartz, MD - Sunnybrook, Toronto Western)

Global Registry: ExAblate 4000 Transcranial MR Guided Focused Ultrasound (TcMRgFUS) of Neurological Disorders (Rambam Medical Center, Sheba Medical Center, Sunnybrook, Swedish Medical Center, University of Virginia, Pennsylvania Hospital, University of Maryland)

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Research Sites

Preclinical*

Columbia University
Johns Hopkins University
Northeastern University
Sunnybrook Health Sciences Centre (Canada)
University of Virginia
Weill Cornell Medical Center (United States)

Clinical

Brigham and Women's Hospital (United States)
Catholic University of Korea
Centro Integral de Neuociencias HM Cinac (Spain)
Mayo Clinic
Ohio State Wexner Medical Center
Pennsylvania Hospital
Rambam Medical Center (Israel)
Severance Hospital (South Korea)
St. Mary's Hospital (United Kingdom)
Stanford University School of Medicine
Sunnybrook Health Sciences Centre (Canada)
Swedish Medical Center, Neuroscience Institute (United States)
Tokyo Women's Hospital (Japan)
Toronto Western Hospital (Canada)
Universitats-Kinderspital Zurich FUS-Center (Switzerland)
University of Maryland School of Medicine
University of Toronto (Canada)
University of Virginia
Yonsei University Health System, Severance Hospital (Korea)
Weill Cornell Medical Center (United States)

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

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Commercial Treatment Sites

Brigham and Women's Hospital (United States)

Centre Medic Diagostic Alomar, ResoFus Alomar (Spain)

Centro Integral de Neurociencias HM Cinac (Spain)

Kantonsspital St. Gallen (Switzerland)

Mayo Clinic

Ohio State University

Pennsylvania Hospital

Rambam Medical center (Israel)

Sonimodul, AG (Switzerland)

St. Mary's Hospital (United Kingdom)

Stanford Medical Group

Swedish Medical Center (United States)

Universita degli Studi di Palermo (Italy)

Universitats-Kinderspital Zurich FUS-Center (Switzerland)

University of Maryland

University Sperling Medical Group (United States)

University of Utah

University of Virginia

Weill Cornell Medical Center (United States)

Manufacturers

Artenga | Ottawa, ON, Canada, www.artenga.com

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

Focused Ultrasound *for Parkinson's Disease*

Media

Colorado Springs Parkinson's sufferer 'won the lottery' with experimental treatment
Colorado Springs Gazette – December 9, 2018

> "No question, focused ultrasound allowed me to keep living my life, keep working, exercising, doing what I'm doing," [Ron Nickelson] said.

Roanoke native gains FDA approval to treat Parkinson's tremors with focused sound waves
Roanoke Times – December 21, 2018

> Elias said the procedure will give Parkinson's patients whose tremors are no longer controlled by medication the option of trying a less invasive procedure than deep brain stimulation.

UVa study: Focused ultrasound's benefits extend to quality of life, mood
The Daily Progress – November 11, 2018

> Participants also reported improved emotional well-being and ability to perform simple tasks and lower incidence of depression and anxiety, [Dr. Jeff Elias] said.

Ultrasound targeting the brain is poised to revolutionize the treatment for Parkinson's disease
CNBC – May 9, 2018

> By destroying or disrupting certain tissues in the brain, focused ultrasound kills abnormal cells and breaks the brain circuits causing the tremor.

Ultrasound Could Offer Noninvasive Treatment for Parkinson's and Depression
Scientific American – November 30, 2017

> Howard Eisenberg, professor and chief of neurosurgery at the University of Maryland School of Medicine, participated in the clinical studies of FUS as an ablative treatment for essential tremor and Parkinson's disease, targeting different brain areas for each disorder. He has found that patients like the technology because it's less invasive than deep brain stimulation, which requires surgery to implant an electrode. "It's not surgery really," says Eisenberg.

Focused Ultrasound *for Parkinson's Disease*

Videos

Kimberly Spletter: Parkinson's patient, University of Maryland:

Ron Nickelson, Parkinson's patient, The Ohio State University Wexner Medical Center:

To view these and other videos about focused ultrasound technology and patients, visit https://www.fusfoundation.org/the-foundation/news-media/multimedia

Key Publications

Gallay MN, Moser D, Federau C and Jeanmonod D (2019) Anatomical and Technical Reappraisal of the Pallidothalamic Tractotomy With the Incisionless Transcranial MR-Guided Focused Ultrasound. A Technical Note. Front. Surg. 6:2. doi: 10.3389/fsurg.2019.00002 published: 24 January 2019 doi: 10.3389/fsurg.2019.00002.

Niu J, Xie J, Guo K, Zhang X, Xia F, Zhao X, Song L, Zhuge D, Li X, Zhao Y, Huang Z. Efficient treatment of Parkinson's disease using ultrasonography-guided rhFGF20 proteoliposomes. Drug Deliv. 2018 Nov;25(1):1560-1569. doi: 10.1080/10717544.2018.1482972.

Jung NY, Park CK, Kim M, Lee PH, Sohn YH, Chang JW. The efficacy and limits of magnetic resonance-guided focused ultrasound pallidotomy for Parkinson's disease: a Phase I clinical trial. J Neurosurg. 2018 Aug 1:1-9. doi: 10.3171/2018.2.JNS172514.

Yue P, Gao L, Wang X, Ding X, Teng J. Ultrasound-triggered effects of the microbubbles coupled to GDNF- and Nurr1-loaded PEGylated liposomes in a rat model of Parkinson's disease. J Cell Biochem. 2018 Jun;119(6):4581-4591. doi: 10.1002/jcb.26608.

Marc N. Gallay, MD, David Moser, BSc, and Daniel Jeanmonod, MD. Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments. J Neurosurg May 25, 2018; DOI: 10.3171/2017.12.

Meng Y, Voisin MR, Suppiah S, Kalia SK, Kalia LV, Hamani C, Lipsman N. Is there a role for MR-guided focused ultrasound in Parkinson's disease? Mov Disord. 2018 Apr;33(4):575-579. doi: 10.1002/mds.27308.

Ito H, Fukutake S, Yamamoto K, Yamaguchi T, Taira T, Kamei T. Magnetic Resonance Imaging-guided Focused Ultrasound Thalamotomy for Parkinson's Disease. Intern Med. 2018 Apr 1;57(7):1027-1031. doi: 10.2169/internalmedicine.9586-17.

Fasano A, De Vloo P, Llinas M, Hlasny E, Kucharczyk W, Hamani C, Lozano AM. Magnetic resonance imaging-guided focused ultrasound thalamotomy in Parkinson tremor: Reoperation after benefit decay. Mov Disord. 2018 Mar 23. doi: 10.1002/mds.27348.

Bretsztajn L, Gedroyc W. Brain-focussed ultrasound: what's the "FUS" all about? A review of current and emerging neurological applications. Br J Radiol. 2018 Mar 6:20170481. doi: 10.1259/bjr.20170481.

Martínez-Fernández R, Rodríguez-Rojas R, Del Álamo M, Hernández-Fernández F, Pineda-Pardo JA, Dileone M, Alonso-Frech F, Foffani G, Obeso I, Gasca-Salas C, de Luis-Pastor E, Vela L, Obeso JA.Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. Lancet Neurol. 2018 Jan;17(1):54-63. doi: 10.1016/S1474-4422(17)30403-9.

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Key Publications

Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial. Bond AE, Shah BB, Huss DS, Dallapiazza RF, Warren A, Harrison MB, Sperling SA, Wang XQ, Gwinn R, Witt J, Ro S, Elias WJ. JAMA Neurol. 2017 Dec 1;74(12):1412-1418. doi: 10.1001/jamaneurol.2017.3098.

Zhang, Hairong & S. Sanchez, Carlos & Kwon, Nancy & R. Jackson-Lewis, Vernice & Przedborski, Serge & Konofagou, Elisa. (2017). Focused-ultrasound mediated anti-alpha-synuclein antibody delivery for the treatment of Parkinson's disease. The Journal of the Acoustical Society of America. 142. 2721-2721. 10.1121/1.5014928. Published Online: 16 November 2017

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Fan CH, Lin CY, Liu HL, Yeh CK. J Control Release. 2017 Sep 10;261:246-262. doi: 10.1016/j.jconrel.2017.07.004. Epub 2017 Jul 8. Review.

Mead BP, Kim N, Miller GW, Hodges D, Mastorakos P, Klibanov AL, Mandell JW, Hirsh J, Suk JS, Hanes J, Price RJ. Novel Focused Ultrasound Gene Therapy Approach Noninvasively Restores Dopaminergic Neuron Function in a Rat Parkinson's Disease Model. Nano Lett. 2017 Jun 14;17(6):3533-3542. doi: 10.1021/acs.nanolett.7b00616. Epub 2017 May 18.

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Schlesinger I, Sinai A, Zaaroor M. Parkinsons Dis. 2017;2017:8124624. doi: 10.1155/2017/8124624. Epub 2017 Mar 30. Review.

Zaaroor M, Sinai A, Goldsher D, Eran A, Nassar M, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. J Neurosurg. 2017 Feb 24:1-9. doi: 10.3171/2016.10.JNS16758.

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Non-invasive, neuron-specific gene therapy by focused ultrasound-induced blood-brain barrier opening in Parkinson's disease mouse model. Lin CY, Hsieh HY, Chen CM, Wu SR, Tsai CH, Huang CY, Hua MY, Wei KC, Yeh CK, Liu HL. J Control Release. 2016 Aug 10;235:72-81. doi: 10.1016/j.jconrel.2016.05.052. Epub 2016 May 26.

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Samiotaki G, Acosta C, Wang S, Konofagou EE. Enhanced delivery and bioactivity of the neurturin neurotrophic factor through focused ultrasound-mediated blood--brain barrier opening in vivo. J Cereb Blood Flow Metab. 2015 Mar 31;35(4):611-22. doi: 10.1038/jcbfm.2014.236.

Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D; First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. Journal of Therapeutic Ultrasound 2014, 2:11