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. 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 Parkinson's disease without incisions or radiation.

## Benefits

Currently, there is no cure for Parkinson's disease. Treatment options include drug therapies and in select patients, surgeries such as deep brain stimulation or radiofrequency ablation.

Focused ultrasound has the ability to noninvasively treat some Parkinson's disease patients through thermal ablation of the brain circuits 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, allowing the diffusion of medications and antibodies into the brain that can potentially prevent progression and/or restore function.

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
- **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

In December 2018, the FDA approved the use of focused ultrasound to treat patients with tremor dominant Parkinson's disease.

Clinical trials are now underway to evaluate if additional symptoms from Parkinson's disease such as dyskinesia and involuntary movements can be treated with focused ultrasound ablation of targeted tissues at various anatomical sites. So far, one side of the brain has been safely treated, and projects will soon assess the ability to treat both sides of the brain with staged treatments.

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 to help treat the dementia associated with Parkinson's disease.

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 the degeneration of nerves within the brain, and even promote healthy nerve tissue regeneration.

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

**Focused Ultrasound Foundation**

For more information, visit **www.fusfoundation.org**

1230 Cedars Court , Suite 206 | Charlottesville, VA 22903 | 434.220.4993

FOCUSED ULTRASOUND FOUNDATION

# Focused Ultrasound *for Parkinson's Disease*

## 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 glioblastoma.

### TISSUE DESTRUCTION

- **Thermal Ablation**: coagulative cell death

### 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

### IMMUNOMODULATION

- Enhanced production and delivery of the body's naturally produced antibodies

### NEUROMODULATION

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

## Research Project Inventory

**Clinical Trials**

A 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 (Sunnybrook Health Sciences Research Centre)

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 (Multi-center: Stanford University, University of Maryland, Brigham and Women's Hospital, Ohio State University, University of Virginia, Mayo Clinic, University of Pennsylvania, Swedish Neuroscience Institute, Toronto Western Hospital, Rambam Medical Center, Severance Hospital, 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 (Centro Integral de Neurociencias HM Cinac)

* 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 (Multi-center: Stanford University, University of Maryland, Brigham and Women's Hospital, Ohio State University, University of Virginia)

* 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 the Initial Effectiveness of ExAblate Transcranial MRgFUS for Unilateral Thalamotomy in the Treatment of Medication Refractory Tremor Dominant Idiopathic Parkinson's Disease (Multi-center: Provincial Peoples Hospital China, Shonan Fujisawa Tokushukai Hospital, Japan).

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 (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 (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 (Centro Integral de Neurociencias HM Cinac)

A Pilot Clinical Trial of the Feasibility, Safety, and Efficacy of Subthalamotomy using ExABlate Transcranial System to Treat Cardinal Motor Features of Parkinson's Disease (Centro Integral de Neurociencias HM Cinac)

A Feasibility Study on the Safety and Preliminary Efficacy of Bilateral Subthalamotomy Using ExAblate Transcranial System to Treat the Cardinal Motor Features of Parkinson's Disease (Centro Integral de Neurociencias HM Cinac)

*Functional Neuroimaging Feedback for Focused Ultrasound Thalamotomy for Tremor Surgery (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 (Rambam Medical Center)

A Feasibility Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MRgFUS for Unilateral Thalamototmy in the Treatment of Medication Refractory Tremor Dominant Idiopathic Parkinson's Disease (Multi-center: University of Virginia, Swedish Medical Center)

A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders (Multi-center: Sunnybrook Health Sciences Centre, Toronto Western)

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

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

FOCUSED ULTRASOUND FOUNDATION

# Focused Ultrasound *for Parkinson's Disease*

## Research Project Inventory

**Preclinical Studies**

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

* Antibody Delivery Through the BBB Opening in an Alpha-Synuclein Model (Columbia University)

*Focused Ultrasound for Increased Delivery of Intranasal DNA Nanoparticles to Rat Brain (Northeastern University)

*Functional Neuroimaging Feedback for Focused Ultrasound Thalamotomy for Tremor Surgery (Ohio State University)

*MRgFUS Gene Delivery for Neuroprotection in Parkinson's Disease (Weill Cornell Medical Center)

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

# Focused Ultrasound *for Parkinson's Disease*

## Research Sites

**Clinical Trials**

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

**Preclinical laboratories**

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

FOCUSED ULTRASOUND FOUNDATION

# Focused Ultrasound *for Parkinson's Disease*

## 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 (United States)

Ohio State University (United States)

Rambam Medical Center (Israel)

Sonimodul, AG (Switzerland)

St. Mary's Hospital (United Kingdom)

Stanford University (United States)

Sunnybrook Health Sciences Research Centre (Canada)

Swedish Medical Center (United States)

Universita degli Studi di Palermo (Italy)

Universitats-Kinderspital Zurich FUS-Center (Switzerland)

University of Maryland (United States)

University of Pennsylvania (United States)

University Sperling Medical Group (United States)

University of Utah (United States)

University of Virginia (United States)

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

**Ultrasound Treatment Might Ease Parkinson's Tremors**
WebMD – November 27, 2019

> "The clinical application of this technique for neurological diseases is an absolute novelty. Few patients know of this treatment option so far, and there are not many specialized centers equipped with the required technology." - Dr. Federico Bruno, University of L'Aquila in Italy.

**Focused Ultrasound Treats Tremors from Parkinson's Disease**
Philadelphia Tribune – July 22, 2019

> "After three hours, Collier came out of the MRI. The procedure targeted the part of his brain giving him a tremor in his right hand. That hand was now still, unlike his trembling left hand."

**How Ultrasound Could Help Curb Parkinson's**
Medical News Today – June 10, 2019

> "We were able to curb the rapid progression of neurodegeneration while improving the neuronal function. We expect our study will open new therapeutic avenues for the early treatment of central nervous system diseases." – Dr. Elisa Konofagou, Colombia University

**Parkinson's Tremors Vanish with Incisionless Surgery**
HealthLeaders Media – April 30, 2019

> "We're still in the early stages of this technology, and I think there's going to be a lot of development in terms of what can be done with it." – Dr. Gordon H. Baltuch, University of Pennsylvania Perelman School of Medicine.

**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.

# 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

FOCUSED ULTRASOUND FOUNDATION

# Focused Ultrasound *for Parkinson's Disease*

## Key Publications


Gallay M, Moser D, Rossi F, Magara, A, et al. MRgFUS Pallidothalamic Tractotomy for Chronic Therapy Resistant Parkinson's Disease in 51 Consecutive Patients: Single Center Experience. Frontiers in Surgery 2020;6 Article 76 doi: 10.3389/fsurg.2019.00076

Rodriguez-Rojas R, Pineda-Pardo JA, Martinez-Fernandez R, Kogan RV, Sanchez-Catasus CA, et al. Functional impact of subthalamotomy by magnetic resonance-guided focused ultrasound in Parkinson's disease: a hybrid PET/MR study of resting-state brain metabolism. Eur J Nucl Med Mol Imaging 2020;47(2):425–36.

LeWitt PA, Lipsman N, Kordower JH. Focused ultrasound opening of the blood–brain barrier for treatment of Parkinson's disease. Mov Disord Hoboken 2019;34(9):1274–8.

Todd N, Zhang Y, Power C, Becerra L, Borsook D, Livingstone M, et al. Modulation of brain function by targeted delivery of GABA through the disrupted blood-brain barrier. NeuroImage Amst 2019;189:267–75.

Ji R, Smith R, Niimi Y, Karakatsani ME, Murillo MF, Jackson-Lewis V, Przedborski S, Konofagou EE. Focused ultrasound enhanced intranasal delivery of brain derived neurotrophic factor produces neurorestorative effects in a Parkinson's disease mouse model. Sci Rep Nat Publ Group Lond 2019;9:1–13.

Ricardo Y, Pavon N, Alvarez L, Casabona E, Teijeiro J, Díaz A, et al. Long-term effect of unilateral subthalamotomy for Parkinson's disease. J Neurol Neurosurg Psychiatry Lond 2019;90(12):1380.

Price RJ, Fisher DG, Jung SS, Hanes J, Ko HS, Kordower JH. Parkinson's disease gene therapy: Will focused ultrasound and nanovectors be the next frontier? Mov Disord Hoboken 2019;34(9):1279–82.

Foffani G, Trigo-Damas I, Pineda-Pardo JA, Blesa J, Radriguez-Rojas R, Martinez-Fernandez R, Obeso JA. Focused ultrasound in Parkinson's disease: A twofold path toward disease modification. Mov Disord Hoboken 2019 ;34(9):1262–73.

Karakatsani ME, Blesa J, JonofagouEE. Blood–brain barrier opening with focused ultrasound in experimental models of Parkinson's disease. Mov Disord Hoboken 2019;34(9):1252–61.

Moosa S, Martínez-Fernández R, Elias WJ, Alamo M del, Eisenberg HM, Fishman PS. The role of high-intensity focused ultrasound as a symptomatic treatment for Parkinson's disease. Mov Disord Hoboken 2019;34(9):1243–51.

Xu Y, He Q, Wang M, Gao Y, Liu X, Li D, et al. Safety and efficacy of magnetic resonance imaging-guided focused ultrasound neurosurgery for Parkinson's disease: a systematic review. Neurosurg Rev 2019; E pub.

Gallay MN, Moser D, Federau C and Jeanmonod D. Anatomical and Technical Reappraisal of the Pallidothalamic Tractotomy With the Incisionless Transcranial MR-Guided Focused Ultrasound. A Technical Note. Front Surg 2019;6:2.

FOCUSED ULTRASOUND FOUNDATION

# Focused Ultrasound *for Parkinson's Disease*

## Key Publications


Fishman P, Lipsman N. Focused ultrasound as an evolving therapy for Parkinson's disease. Mov Disord Off J Mov Disord Soc 2019;34(9):1241–2.

Xhima K, Nabbouh F, Hynynen K, Aubert I, Tandon A. Noninvasive delivery of an α-synuclein gene silencing vector with magnetic resonance-guided focused ultrasound. Mov Disord Off J Mov Disord Soc 2018;33(10):1567–79.

Niethammer M, Tang CC, Vo A, Nguyen N, Spetsieris P, Dhawan V, et al. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. Sci Transl Med 2018 28;10(469).

Zhang H, Sierra C, Kwon N, Karakatsani ME, Jackson-Lewis VR, Przedborski S, et al. Focused-ultrasound Mediated Anti-Alpha-Synuclein Antibody Delivery for the Treat

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;25(1):1560-1569.

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;1:1-9.

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;119(6):4581-4591.

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;33(4):575-579.

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;57(7):1027-1031.

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; 33(5):848-849.

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;17(1):54-63.

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 2018; 128(1):202-210.

# Focused Ultrasound *for Parkinson's Disease*

## Key Publications


Bond AE, Shah BB, Huss DS, Dallapiazza RF, Warren A, Harrison MB, et al. Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol 2017;74(12):1412-1418.

Fan CH, Lin CY, Liu HL, Yeh CK.Ultrasound targeted CNS gene delivery for Parkinson's disease treatment. J Control Release 2017;261:246-262.

Mead BP, Kim N, Miller GW, Hodges D, Mastorakos P, Klibanov AL, et al. Novel Focused Ultrasound Gene Therapy Approach Noninvasively Restores Dopaminergic Neuron Function in a Rat Parkinson's Disease Model. Nano Lett 2017;17(6):3533-3542.

Long L, Cai X, Guo R, Wang P, Wu L, Yin T, Liao S, Lu Z. Treatment of Parkinson's disease in rats by Nrf2 transfection using MRI-guided focused ultrasound delivery of nanomicrobubbles. Biochem Biophys Res Commun 2017;482(1):75-80.

Lin CY, Hsieh HY, Chen CM, Wu SR, Tsai CH, Huang CY, et al. Non-invasive, neuron-specific gene therapy by focused ultrasound-induced blood-brain barrier opening in Parkinson's disease mouse model. J Control Release 2016;235:72-81.

Fan CH, Ting CY, Lin CY, Chan HL, Chang YC, Chen YY, Liu HL, Yeh CK. Noninvasive, Targeted, and Non-Viral Ultrasound-Mediated GDNF-Plasmid Delivery for Treatment of Parkinson's Disease. Sci Rep 2016;6:19579.

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;35(4):611-22.