FOCUSED ULTRASOUND FOUNDATION

Focused Ultrasound for Glioblastoma

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 primary brain tumors such as glioblastoma. This novel technology precisely focuses beams of ultrasound energy on targets in the brain without damaging surrounding normal tissue. Where the beams converge, the ultrasound produces a variety of effects on tissue enabling treatment of the targeted areas.

Benefits

Currently, there is no cure for glioblastoma, and treatment options include surgery, radiation therapy, chemotherapy and immunotherapy. These treatments have limited efficacy and are associated with significant side effects. Focused ultrasound has the potential to offer an alternative or complement to the above therapies.

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 directly to the brain target site
- No ionizing radiation - fewer side effects and can be safely repeated

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
- Histotripsy: mechanical cell disruption
- Sonodynamic therapy: activation of cell toxic drugs
- Microvascular occlusion: ischemic 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

- Tumor cell disruption: exposure of tumor antigens leads to immune cell trafficking to the tumor
- Immune cell trafficking: enhanced delivery of immune cells to the target site
- Augmentation of immunotherapy drugs
- Enhanced drug delivery

RADIATION

- Decreased radiation dose: tumor preconditioning and sensitization

For more information, visit www.fusfoundation.org

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State of the Field

There are three technical approaches used to deliver focused ultrasound to brain tissue to treat glioblastoma. The first and most well studied technique uses MRI-guidance, the second utilizes neuro-navigation guidance and the third is not image guided but involves the implantation of an ultrasound device into the skull.

A majority of the clinical research regarding focused ultrasound for the treatment of glioblastoma concentrates on enhancing the delivery of chemotherapy and/or immunotherapeutic agents to the tumor and surrounding brain tissue using focused ultrasound mediated blood-brain barrier (BBB) opening.

MRI-guided focused ultrasound induced blood-brain barrier opening has already proven to be safe and effective and there are now ongoing clinical trials studying repeated BBB opening in combination with chemotherapy and immunotherapy for the treatment of glioblastoma.

The clinical trial to determine the safety of blood brain barrier opening using the neuro-navigation guided focused ultrasound system (NaviFUS) was recently completed and publication of the results are forthcoming. The company now has an active clinical trial in glioblastoma patients to prove the efficacy of this device in combination with chemotherapy. Additional planned clinical trials using the NaviFUS system in patients with GBMs include a radiation enhancement study and a sonodynamic therapy (tissue destruction) study.

The clinical trial to determine the safety and efficacy of the surgically implanted medical device, called the SonoCloud9 by CarThera, is ongoing. Once implanted, this device is able to repeatedly deliver ultrasound energy to brain tumors to enhance the delivery or chemotherapy and immunotherapeutics via BBB opening, and possibly facilitate sonodynamic therapy.

There are a plethora of preclinical laboratory studies testing some of focused ultrasound's other biomechanisms for the treatment of glioblastomas. Such studies are examining the ability of focused ultrasound to locally activate cytotoxic agents (sonodynamic therapy), enhance the effectiveness of radiation (radiosensitization), and destroy tumor cells through disruption of blood vessels locally releasing encapsulated therapies using microbubbles.

Additional preclinical studies are evaluating the immunomodulatory effects of FUS when applied to intracranial gliomas and the ability of histotripsy to destroy brain tumors in a rapid and precise fashion.

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Research Project Inventory

Clinical Trials

*Assessment of Safety and Feasibility of ExAblate Blood-Brain Barrier (BBB) Disruption for Treatment of Glioma (Sunnybrook Health Sciences Centre, Canada)

*Assessment of Safety and Fesibility of ExAblate Blood-Brain Barrier (BBB) Disruption (Multisite: University of Maryland, Brigham and Women's, University of Virginia, West Virginia University)

Safety and Feasibility of ExAblate Blood-Brain Barrier Disruption for the Treatment of Glioblastoma in Patients Undergoing Standard Chemotherapy (Severance Hospital, Korea)

*ExAblate Blood-Brain Barrier Disruption with Carboplatin for the Treatment of rGBM (Sunnybrook Health Sciences Centre (Canada), Yonsei University Medical Center (Korea))

Safety and Efficacy of Transient Opening of the Blood-brain Barrier (BBB) with the SonoCloud-9 (SC9-GBM-01) (Multi-site: United States and France)

Innovative SonoCloud-9 Device for Blood-Brain Barrier Opening in First-Line Temozolamide Glioblastoma Patients (Multi-site: Belgium, France and Switzerland)

Ultrasound-based Blood-brain Barrier Opening and Albumin-bound Paclitaxel for Recurrent Glioblastoma (SC9/ABX) (Northwestern Memorial Hospital, Chicago, IL, United States)

*Efficacy and Safety of NaviFUS System add-on Bevacizumab (BEV) in recurrent GBM patients (Linkou Chang Gung Memorial Hospital, Taiwan)

Exablate Blood-Brain Barrier Disruption for the treatment of rGBM in Subjects Undergoing Carboplatin Monotherapy (Stanford, University of Maryland, Brigham and Women's, Cleveland Clinic)

*Sonodynamic Therapy with ExAblate System in Glioblastoma Patients (Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Italy)

Study of Sonodynamic Therapy in Participants with Recurrent High-Grade Glioma (St. Joseph's Hospital and Medical Center, Phoenix, AZ, United States)

ˆNaviFUS-induced BBB opening and 5-ALA in Glioblastoma (Taiwan)

ˆNaviFUS-induced BBB opening and radiation therapy for glipblastoma treatment (Taiwan)

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

ˆClinical trials in the concept development phase

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Research Project Inventory

Preclinical Laboratory Studies

*Safety evaluation of irinotecan delivery to a rat glioma model using a clinical MRI-guided system (Brigham and Women's Hospital)

*Microvascular Ablation of Intracranial Gliomas with Focused Ultrasound (University of Virginia Health System)

*Focused ultrasound radiosensitization of brain tumors (University of Virginia Health System)

*Ultrasound-mediated delivery of siRNA for enhancing temozolomide efficacy against glioblastoma (Boston University)

*Focused Ultrasound Immunomodulation in a Mouse GL261 Intracranial Glioma (Multi-site consortium)

*Acoustic activation of the GBM-brain microenvironment for improved T-cell immunotherapy (University of Maryland)

*Ultrasound enabled detection of circulating tumor biomarkers for glioblastoma (Northwestern University)

*Immunologic and genomic effects of focused ultrasound in glioblastoma (Washington University)

Chemotherapy sensitization of glioblastoma by focused ultrasound-mediated delivery of therapeutic liposomes (ETH Zurich)

Sonodynamic Therapy on Intracranial Glioblastoma Xenografts Using Sinoporphyrin Sodium Delivered by Ultrasound with Microbubbles (Shenzhen University)

Enhancing glioblastoma treatment using cisplatin-gold-nanoparticle conjugates and targeted delivery with magnetic resonance-guided focused ultrasound (Hospital for Sick Children)

Enhanced delivery of paclitaxel liposomes using focused ultrasoundwith microbubbles for treating nude mice bearing intracranial glioblastoma xenografts (Chinese Academy of Sciences)

Focused Ultrasound Enhances Central Nervous System Delivery of Bevacizumab for Malignant Glioma Treatment (Chang Gung Memorial Hospital)

Prolonged survival upon ultrasound-enhanced doxorubicin delivery in two syngeneic glioblastoma mouse models (University Children's Hospital Zurich)

Focused ultrasound and interleukin-4 receptor-targeted liposomal doxorubicin for enhanced targeted drug delivery and antitumor effect in glioblastoma multiforme (National Yang-Ming University)

*Histotripsy in Naturally Occurring Canine Brain Tumors (Virginia-Maryland College of Veterinary Medicine)

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

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Research Sites

Clinical Trials

- AP-HM, La Timone, Hôpital Universitaire (France)
- Brigham and Women's Hospital (United States)
- Centre hospitalier Universitaire d'Angers (France)
- Centre hospitalier universitaire vaudois CHUV (Switzerland)
- Chang Gung Memorial Hospital, Taoyuan (Taiwan)
- Cleveland Clinic (United States)
- Groupe Hospitalier Saint-André (France)
- Hôpitaux Universitaires Pitié-Salpêtrière (France)
- Hôpital de La Timone (France)
- Hospices Civils de Lyon, Hôpital Pierre Wertheimer (France)
- Kantonsspital Aarau (Switzerland)
- Katholieke Universiteit Leuven (Belgium)
- MD Anderson Cancer Center (United States)
- Northwestern University (United States)
- Pitié Salpêtrière Hospital (France)
- St. Mary's Hospital (United Kingdom)
- Stanford University (United States)
- Sunnybrook Health Sciences Centre (Canada)
- Università degli Studi di Palermo (Italy)
- University of Maryland School of Medicine (United States)
- University of Virginia (United States)
- West Virginia University (United States)
- Yonsei University Medical Center (Korea)

Preclinical Laboratories

- Chang Gung University (Taiwan)
- Chinese Academy of Sciences, Shenzhen Institutes of Advanced Technology (China)
- Fralin Biomedical Research Institute at Virginia Tech Carilion (United States)
- Georgia Institute of Technology (United States)
- Hôpitaux Universitaires Pitié-Salpêtrière (France)
- Institute of Cancer Research (United Kingdom)
- MD Anderson Cancer Center (United States)
- Medical University of South Carolina (United States)
- Seoul National University Hospital (South Korea)
- Stanford University School of Medicine (United States)

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Research Sites

Preclinical Laboratories (Cont.)

- State University of New York Upstate Medical University (United States)
- Sunnybrook Health Sciences Centre (Canada)
- Universität Heidelberg (Germany)
- Universitäts-Kinderspital Zürich, FUS-Center (Switzerland)
- Universitätsklinik Leipzig (Germany)
- University of California, Los Angeles (United States)
- University of California, San Diego School of Medicine (United States)
- University of Dundee, Institute for Medical Science and Technology (United Kingdom)
- University of Maryland School of Medicine (United States)
- University of Michigan (United States)
- University of North Carolina at Chapel Hill (United States)
- University of Oxford (United Kingdom)
- University of Virginia Health System (United States)
- Virginia-Maryland College of Veterinary Medicine (United States)
- Wake Forest University Baptist Medical Center (United States)
- Washington University in St. Louis (United States)
- Wenzhou Medical University (China)

Manufacturers

CarThera | Paris, France | www.carthera.eu

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

NaviFUS | New Taipei City, Taiwan | www.navifus.com

Therawave, LLC | New York, NY, United States

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Media

[Ultrasound implant helps potent cancer drug cross blood-brain barrier]
New Atlas – December 12, 2019

> A new study from Northwestern University is demonstrating evidence a novel implantable ultrasound device allows a less toxic formulation of chemotherapy to cross the blood-brain barrier and destroy deadly tumors.

[Treating brain Tumours with Ultrasound: This Could Be the Next Frontier in Cancer Treatment]
Sunnybrook - Your Health Matters – October 10, 2019

> "In Phase 1 of this study, we found we can safely open the blood-brain barrier. It's quick, reversible and we don't see any major adverse effects," says Dr. Nir Lipsman, principal investigator and director at Sunnybrook's Harquail Centre for Neuromodulation.

[University of Maryland Study Uses Tiny Bubbles in Hopes of Getting Cancer-Fighting Drugs Inside the Brain]
Baltimore Sun – October 2, 2019

> "Normally, chemotherapy gets in a little but not a lot." "In the future, we're hoping we can provide our drugs of choice a way to get in. We're hoping we can use it for lots of things." - Dr. Graeme Woodworth, Director of the Brain Tumor Treatment and Research Center at the University of Maryland Medical Center

[Focused ultrasounds allow scalpel-free brain surgery]
Globe and Mail – January 1, 2019

> "We've been doing surgery on the brain for decades, but this technology allows us to do so without going through the skull and healthy brain, which causes a lot of damage along the way. It's a new way of doing something old." - Dr. Anthony Levitt, chief of the Hurvitz Brain Sciences Centre at Sunnybrook Health Sciences Centre in Toronto

[Bypassing the Blood-Brain Barrier]
Psychology Today – November 6, 2018

> "We're very close to getting there, I think we're certainly going to see exciting things in the next 10 years." – Dr. Graeme Woodworth, Director of the Brain Tumor Treatment and Research Center at the University of Maryland Medical Center

[Brain cancer treatments showing promise with targeted therapies. 'Very exciting stuff.']
Miami Herald – May 25, 2018

> "The beauty of this is that it lets you target an area of the brain causing the problem ... and without opening the skin or skull or putting anything into the brain, you can destroy the part of the brain that's sick. That's a first. This involved no radiation. When the children wake up [after the ultrasound treatment], they are normal — they sit up and have supper and go home the next day." - Dr. John Ragheb, a neurosurgeon and director of neurology at Nicklaus Children's Hospital

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Key Publications

Park SH, Kim MJ, Jung HH, Chang WS, Choi HS, Rachmilevitch I, et al. Safety and feasibility of multiple blood-brain barrier disruptions for the treatment of glioblastoma in patients undergoing standard adjuvant chemotherapy. J Neurosurg. 2020 Jan 3;1–9.

Mainprize T, Lipsman N, Huang YH, Meng Y, Bethune A, Ironside S, et al. Blood Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study. Scientific Reports 2019;9:321.

Idbaih A, Canney M, Belin L, Desseaux C, Vignot A, Bouchoux G, et al. Safety and Feasibility of Repeated and Transient Blood-Brain Barrier Disruption by Pulsed Ultrasound in Patients with Recurrent Glioblastoma. Clinical Cancer Research 2019.

Pi Z, Huang Y, Shen Y, Zeng X,Hu Y, Chen T, et al. Sonodynamic Therapy on Intracranial Glioblastoma Xenografts Using Sinoporphyrin Sodium Delivered by Ultrasound with Microbubbles. Ann Biomed Eng 2019;47:549–562.

Fan C-H, Wang T-W, Hsieh Y-K, Wang C-F, Gao Z, Kim A, et al. Enhancing Boron Uptake in Brain Glioma by a Boron-Polymer/Microbubble Complex with Focused Ultrasound. ACS Appl Mater Interfaces 2019;11(12):11144–56.

Deng Z, Sheng Z, Yan F. Ultrasound-Induced Blood-Brain-Barrier Opening Enhances Anticancer Efficacy in the Treatment of Glioblastoma: Current Status and Future Prospects. J Oncol 2019;2019:2345203.

Asquier N, Bouchoux G, Canney M, Martin C, Law-Ye B, Leclercq D, et al. Blood Brain Barrier Disruption in Humans Using an Implantable Ultrasound Device: Quantification with MR images and Correlation with Local Acoustic Pressure. J Neurosurg. 2019;1-9.

Drean A, Lemaire N, Bouchoux G, Goldwirt L, Canney M, Goli L, et al. Temporary Blood Brain Barrier Disruption by Low Intensity Pulsed Ultraosund Increases Carboplatin Delivery and Efficacy in Preclinical Models of Glioblastoma. J Neurooncol 2019; 144(1):33-41.

Wan Q, Zou C, Hu D, Zhou J, Chen M, Tie C, et al. Imaging-guided focused ultrasound-induced thermal and sonodynamic effects of nanosonosensitizers for synergistic enhancement of glioblastoma therapy. Biomater Sci 2019;7(7):3007–15.

Wu S-K, Santos MA, Marcus SL, Hynynen K. MR-guided Focused Ultrasound Facilitates Sonodynamic Therapy with 5-Aminolevulinic Acid in a Rat Glioma Model. Sci Rep 2019;9(1):10465.

Coluccia D, Figueiredo CA, Wu MY, Riemenschneider AN, Diaz R, Luck A, et al. Enhancing glioblastoma treatment using cisplatin-gold-nanoparticle conjugates and targeted delivery with magnetic resonance-guided focused ultrasound. Nanomedicine Nanotechnol Biol Med 2018;14(4):1137–48.

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Zhu L, Cheng G, Ye D, Nazeri A, Yue Y, Liu W et al. Focused Ultrasound-enabled Brain Tumor Liquid Biopsy. Sci Rep 2018;8:6553.

Lin Y-L, Wu M-T, Yang F-Y. Pharmacokinetics of doxorubicin in glioblastoma multiforme following ultrasound-Induced blood-brain barrier disruption as determined by microdialysis. J Pharm Biomed Anal 2018;149:482–7.

MacDonell J, Patel N, Rubino S, Ghoshal G, Fischer G, Burdette EC, et al. Magnetic resonance-guided interstitial high-intensity focused ultrasound for brain tumor ablation. Neurosurg Focus 2018;44(2):E11.

Carpentier A, Canney M, Vignot A, Reina V, Beccaria K, Horodyckid C, et al. Clinical Trial of Blood Brain Barrier Disruption by Pulsed Ultrasound. Science Translational Medicine 2016;8:343.

Liu HL, Hsu PH, Lin CY, Huang CW, Chai WY, Chu PC, et al. Focused Ultrasound Enhances Central Nervous System Delivery of Bevacizumab for Malignant Glioma Treatment. Radiology 2016;281(1):99-108.

Goldwirt L, Canney M, Horodyckid C, Poupon J, Mourah S, Vignot A, et al. Enhanced brain distribution of carboplatin in a primate model after blood-brain barrier disruption using an implantable ultrasound device. Cancer Chemother Pharmacol 2016;77:211-216.

Cohen-Inbar O, Xu Z, Sheehan JP. Focused ultrasound-aided immunomodulation in glioblastoma multiforme: a therapeutic concept. J Ther Ultrasound 2016;4:2.

Chen PY, Hsieh HY, Huang CY, Lin CY, Wei KC, Liu HL. Focused ultrasound-induced blood-brain barrier opening to enhance interleukin-12 delivery for brain tumor immunotherapy: a preclinical feasibility study. J Transl Med 2015;13:451.