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 deep 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, bleeding or infection**
- **Image guided – precise targeting leads to minimal damage to surrounding normal tissue**
- **Blood brain barrier (BBB) opening – enhancing the delivery of therapeutics directly to the target site**
- **No ionizing radiation – can be safely repeated if necessary**

State of the Field

Much of the clinical research regarding focused ultrasound for the treatment of glioblastoma concentrates on enhancing the delivery of chemotherapy or immunotherapeutic agents to the tumor and surrounding brain tissue using focused ultrasound mediated blood brain barrier opening.

Opening the blood brain barrier was demonstrated to be feasible and safe in a pilot trial of 5 patients with high grade gliomas. There was a trend toward increased concentration of chemotherapy agents in the areas targeted with focused ultrasound compared to non-targeted tissue. Ongoing clinical trials are now examining repeated disruption of the BBB in combination with chemotherapy and immunotherapy to treat glioblastomas.

An additional, yet more invasive approach that is being clinically tested involves implanting a small ultrasound transducer directly into the skull to allow for repeated opening of the BBB in combination with chemotherapy without the need for repeat, oftentimes lengthy procedures under imaging guidance which may prove more convenient for patients.

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), destroy tumor cells through disruption of blood vessels and locally release 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 mechanically destroy brain tumors in a more rapid and precise fashion compared to thermal ablation.

Focused Ultrasound Foundation

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

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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 glioblastomas.

TISSUE DESTRUCTION

- **Thermal Ablation**: coagulative cell death
- **Histotripsy**: mechanical cell disruption

THERAPEUTIC AGENT DELIVERY

- **BBB opening:** increased diffusion of drugs to target site
- **Carrier mediated vehicle:** activate encapsulated therapies
- **Sonodynamic therapy:** activate drugs that cause cell death

IMMUNOMODULATION

- **Tumor cell disruption**: exposure of tumor antigens improves the anti-tumor immune response
- **Immune cell trafficking:** enhanced delivery of immune cells to the target site

RADIATION SENSITIZATION

- **Hyperthermic preconditioning:** increased blood flow enhances treatment, allowing reduced radiation dosing

Research Project Inventory

Preclinical Laboratory Studies

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

*Sonodynamic therapy for treatment of C6 glioma in a rat model proof-of-concept study: Fluorescein (F Prada - University of Virginia Health System)

*Microvascular Ablation of Intracranial Gliomas with Focused Ultrasound (M Kalani, R Price - University of Virginia Health System)

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

*Safety study: sonodynamic therapy with 5-ALA in a porcine model (F Prada - University of Virginia Health System)

*Delivery of Brain Tumor-Penetrating Nanoparticles Across the Blood Brain Barrier with MR-Guided Focused Ultrasound (R Price - University of Virginia Health System)

*Targeted Delivery of Controlled Release Nanoparticles to Brain Tumors Using Contrast Agent Microbubbles and High-Intensity Focused Ultrasound (R Price - University of Virginia Health System)

*Sonodynamic therapy for treatment of C6 glioma in a rat model proof-of-concept study: 5-ALA (Z Xu - University of Virginia Health System)

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

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

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Research Project Inventory

Preclinical Laboratory Studies (Cont.)

*Focused Ultrasound Immunomodulation in a Mouse GL261 Intracranial Glioma (R Price, G Woodworth, C Arvanitis, Z Xu, N McDannold, K Hynynen - Multi-site consortium)

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

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

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

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

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

Prolonged survival upon ultrasound-enhanced doxorubicin delivery in two syngeneic glioblastoma mouse models (M Bernasconi - 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 (M Wei - National Yang-Ming University)

Concurrent blood-brain barrier opening and local drug delivery using drug-carrying microbubbles and focused ultrasound for brain glioma treatment (C Yeh - National Tsing Hua University)

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

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Research Project Inventory

Clinical Trials

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

A FIH Feasibility Study to Evaluate the Safety of Transient Disruption of Blood-brain Barrier in Recurrent Glioblastoma Multiforme (GBM) Patients Using NaviFUS System (K-C Wei - Linkou Chang Gung Memoria Hospital Taiwan)

Assessment of Safety and Feasibility of ExAblate Blood-Brain Barrier Disruption for the Treatment of High Grade Glioma in Patients Undergoing Standard Chemotherapy (T Mainprize - Sunnybrook)

A Study to Evaluate the Safety and Feasibility of Exablate Model 4000 Type-2 to Temporarily Mediate Blood-Brain Barrier Disruption (BBBD) in Patients With Suspected Glioblastoma in the Setting of Planned Surgical Interventions (G Woodworth – University of Maryland)

Assessment of Safety and Feasibility of ExAblate Blood-Brain Barrier Disruption for the Treatment of High Grade Glioma in Patients Undergoing Standard Chemotherapy (G Woodworth – University of Maryland)

Study to Evaluate the Safety and the Efficacy of Transient Opening of the Blood-brain Barrier (BBB) by Low Intensity Pulsed Ultrasound With the SonoCloud-9 Implantable Device in Recurrent Glioblastoma Patients Eligible for Surgery and for Carboplatin Chemotherapy (A Carpentier - Hopitaux Universitarires Pitie-Salpetriere, Inserm LabTAU)

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Research Sites

Preclinical laboratories

Brigham and Women's Hospital (Boston, MA, United States)
Chaim Sheba Medical Center (Tel Hashomer, Israel)
Chang Gung University (Taoyuan City, Taiwan)
Chinese Academy of Sciences, Shenzhen Institutes of Advanced Technology (Shenzhen, China)
Commissariat à l'énergie atomique et aux énergies alternatives (Paris, France)
Deutsches Krebsforschungszentrum (Heidelberg, Germany)
Fralin Biomedical Research Institute at Virginia Tech Carilion (Roanoke, VA, United States)
Georgia Institute of Technology (Atlanta, GA, United States)
Hôpitaux Universitaires Pitié-Salpêtrière (Paris, France)
Hospital for Sick Children (Toronto, Ont., Canada)
Inserm LabTAU (Lyon, France)
Institute of Cancer Research (Sutton, United Kingdom)
Lawson Health Research Institute (London, Ont., Canada)
MD Anderson Cancer Center (Houston, TX, United States)
Medical University of South Carolina (Charleston, SC, United States)
National Tsing Hua University (Hsinchu, Taiwan)
National Yang-Ming University (Beitou District, TAIPEI CITY, Taiwan)
Rostov Scientific Research Institute of Oncology (Rostov-on-Don, Russian Federation)
Seoul National University Hospital (Seoul, South Korea)
Stanford University School of Medicine (Stanford, CA, United States)
State University of New York Upstate Medical University (Albany, NY, United States)
Sunnybrook Health Sciences Centre (Toronto, Ont., Canada)
Universität Heidelberg (Mannheim, Germany)
Universitäts-Kinderspital Zürich, FUS-Center (Zurich, Switzerland)
Universitätsklinik Leipzig (Leipzig, Germany)
University of California, Los Angeles (Los Angeles, CA, United States)
University of California, San Diego School of Medicine (San Diego, CA, United States)
University of Dundee, Institute for Medical Science and Technology (Dundee, United Kingdom)
University of Maryland School of Medicine (Baltimore, MD, United States)
University of Michigan (Ann Arbor, MI, United States)
University of North Carolina at Chapel Hill (Chapel Hill, NC, United States)
University of Oxford (Oxford, United Kingdom)
University of Virginia Health System (Charlottesville, VA, United States)
Wake Forest University Baptist Medical Center (Winston-Salem, NC, United States)
Washington University in St. Louis (St. Louis, MO, United States)
Wenzhou Medical University (Wenzhou, China)

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Clinical trials

Brigham and Women's Hospital (Boston, MA, United States)
Chang Gung Memorial Hospital, Taoyuan (Taoyuan City, Taiwan)
Chang Gung University (Taoyuan City, Taiwan)
Hôpitaux Universitaires Pitié-Salpêtrière (Paris, France)
Inserm LabTAU (Lyon, France)
Kantonsspital Aarau (Aarau, Switzerland)
St. Mary's Hospital (London, United Kingdom)
Sunnybrook Health Sciences Centre (Toronto, Ont., Canada)
Università degli Studi di Palermo (Palermo, Italy)
University of Maryland School of Medicine (Baltimore, MD, United States)

Manufacturers

CarThera | Paris, France, www.carthera.eu

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

NaviFUS | New Taipei City, Taiwan, www.navi-fus.com

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Key Publications

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.

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.

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.

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.

Aryal M, Vykhodtseva N, Zhang YZ,Park J, McDannold N. Multiple treatments with liposomal doxorubicin and ultrasound-induced disruption of blood-tumor and blood-brain barriers improve outcomes in a rat glioma model. J Control Release 2013;169:103-111.

Marty B, Larrat B, Van Landeghem M, Robic C, Robert P, Port M et al. Dynamic study of blood-brain barrier closure after its disruption using ultrasound: a quantitative analysis. J Cereb Blood Flow Metab 2012;32:1948-58.

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Media

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

Focused ultrasound opens the blood-brain barrier
Physics World – January 31, 2018

> "There may be effective agents for many neurodegenerative and other brain disorders, but we just can't get enough drug into the brain to have a meaningful impact. A safe and reversible means of opening the BBB directly at the site of pathology has been a major goal for several decades." – Dr. Nir Lipsman, Sunnybrook Health Sciences Centre

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

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

Getting cancer drugs into the brain
Nature – September 9, 2018

> "Focused ultrasound is a platform technology: a tool that people can use for many different therapies. We're trying to solve this problem once, so we won't have to solve it for everything. And we continue trying to make these treatment devices cheaper and easier to use." - Dr. Kullervo Hynynen, University of Toronto in Canada