Focused Ultrasound and Cancer Immunotherapy

Overview

Focused ultrasound is an early stage, noninvasive therapeutic technology with the potential to improve the quality and longevity of life and decrease the cost of care for patients with cancer. This novel technology precisely focuses beams of ultrasound energy on targets deep within the body without damaging surrounding normal tissue. Where the beams converge, the ultrasound can produce a variety of therapeutic effects on tissue enabling an incisionless treatment.

By harnessing the intrinsic powers of the immune system, immunotherapy treatments have the potential to achieve remission and potentially cure certain cancers. The most promising immunotherapy agents, called checkpoint inhibitors, target specific regulatory checkpoints and ultimately augment the immune system’s attack on the tumor. However, these therapies are only effective in 20-40% of patients. The efficacy of such therapies can be improved in patients with an enhanced immune response prior to treatment, which can be elicited by ablative therapies such as focused ultrasound.

Benefits

Current treatment options for cancer include surgery, chemotherapy and radiation. Focused ultrasound can replace or complement these treatments, either when used alone or in combination with immunotherapies. Focused ultrasound has been shown to enhance the response to immunotherapeutic medications by providing the initial immune response that the drug can then capitalize on. Additionally, focused ultrasound can be used to enhance the delivery of these immunotherapeutics to the tumor.

- **Noninvasive** – no incisions, no risk of infection or bleeding, less pain and rapid recovery
- **Image guided** – minimal damage to surrounding healthy tissue
- **No ionizing radiation** – fewer side effects and can be safely repeated
- **Initiation of an anti-tumor immune response** – destruction of tumor cells leads to exposure of tumor antigens, which can then be recognized and targeted by the body’s immune system
- **Directly enhances the effectiveness of immuno-oncology drugs**

State of the Field

The first two clinical trials pairing focused ultrasound with an immunotherapy drug are underway and actively recruiting patients. These studies at the University of Virginia are investigating the combination of focused ultrasound and pembrolizumab in patients with either metastatic breast cancer or solid tumors.

Preclinical laboratory studies in several other tumor models including melanoma, pancreatic cancer and glioblastoma have demonstrated that focused ultrasound can elicit a powerful anti-tumor immune response either alone or in combination with other immune-based therapies. This research is critical to inform future combination clinical trials.

The Foundation has also established key partnerships with the Cancer Research Institute (CRI) and the Parker Institute for Cancer Immunotherapy (PICI), leading organizations in the field of cancer immunotherapy. Collaborative efforts will help advance more streamlined and rigorous research that will accelerate progress toward clinical trials, while also enabling better standardization in the field and increased consistency of protocols.

For more information, visit www.fusfoundation.org

1230 Cedars Court, Suite 206 | Charlottesville, VA 22903 | 434.220.4993
The Focused Ultrasound Foundation has held three workshops to address key questions involving the use of focused ultrasound for cancer immunotherapy. Each of these workshops brought together critical stakeholders – researchers, clinicians, industry, government, and others – in a small group environment that encouraged free dissemination of information and ideas and fostered a collaborative spirit. Participants critically evaluated the current body of evidence, assessed the value of ongoing work, and created a roadmap of projects to guide the field forward.

In addition to regularly convening the many stakeholders in this space, the Focused Ultrasound Foundation has put together a scientific advisory board to guide the program. These advisory board members have deep expertise in cancer immunotherapy and focused ultrasound and represent the leaders in this field.

- Jill O’Donnell-Tormey, PhD – Cancer Research Institute
- Theresa LaVallee, PhD – Parker Institute for Cancer Immunotherapy
- Tim Bullock, PhD – University of Virginia
- Kathy Ferrara, PhD – Stanford University
- Chandan Guha, MD – Montefiore/Albert Einstein
- Gavin Dunn, MD, PhD – Washington University in St. Louis

The following is a list of mechanisms of action currently being studied for cancer immunotherapy.

**DELIVERY OF THERAPEUTIC AGENTS**

- **BBB opening**: increased diffusion of therapeutics and immune cells to targeted brain tissue
- **Increased vascular permeability**: enhancing the delivery of therapeutics to the target
- **Carrier mediated vehicle**: locally activate encapsulated therapies
- **Stromal disruption**: disturb the tumor microenvironment to permit drug infiltration
- **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
- **Augmentation of immunotherapy drugs**
- **Enhanced drug delivery**

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](http://www.fusfoundation.org/the-technology/mechanisms-of-action)
### Research Project Inventory

<table>
<thead>
<tr>
<th></th>
<th>Preclinical Studies</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>9</strong></td>
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#### Preclinical Studies

- *Focused ultrasound immunomodulation for pancreatic cancer (F Padilla - University of Virginia)*
- *Immunologic and genomic effects of focused ultrasound in glioblastoma (G Dunn – Washington University)*
- *Ultrasound-induced immune response on breast cancer (C Lafon – University of Virginia)*
- *Histotripsy tumor ablation-mediated immune stimulation (Z Xu – University of Michigan)*
- *Focused ultrasound radiosensitization of brain tumors (F Padilla – University of Virginia)*
- *Enhancing immune therapy for brain metastases with focused ultrasound (T Bullock – University of Virginia)*
- *Focused ultrasound Immunomodulation in a Mouse GL261 Intracranial Glioma (R Price, G Woodworth, C Arvanitis, Z Xu, N McDannold, K Hynynen - Multi-site consortium)*
- *Defining Basic Properties of Physical Immunotherapy using HIFU and Immune Checkpoint Inhibition (G ter Haar – Institute of Cancer Research)*
- *Focused ultrasound stimulation of the immune response in cancer models (F Padilla – Inserm LabTau)*
- *Ultrasound ablation combined with immunotherapy: priming to enhance efficacy (K Ferrara – University of California, Davis)*

Relative immunogenicity of various focused ultrasound modes in GBM (Multi-site consortium, concept development)

FUS-induced modulation of immunostimulatory effects of radiation therapy in breast and lung cancer tumor models (Memorial Sloan Kettering, concept development)

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

*Pilot Evaluation Of Safety, Immunologic Effect, And Therapeutic Impact Of Focused Ultrasound Ablation Of Advanced Solid Tumors Alone And In Combination With Pd-1 Antibody Blockade (C Slingluff – University of Virginia)

*Focused Ultrasound Therapy to Augment Antigen Presentation and Immune-Specificity of Checkpoint Inhibitor Therapy with Pembrolizumab for Metastatic Breast Cancer (P Dillon – University of Virginia)

*Adjuvant Focused Ultrasound to Promote Immunotherapy Response for Undifferentiated Pleomorphic Sarcoma (M Bucknor – University of California, San Francisco)

*Measure immune response induced by FUS ablation for pancreatic cancer (Multi-site consortium)

Promotion of the immune response in patients treated by HIFU for prostate cancer (F Padilla – Hospices Civils de Lyon)

Focused ultrasound for the treatment of brain metastases (C Slingluff – University of Virginia, concept development)

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

Preclinical

Albert Einstein College of Medicine (New York, NY, United States)
Brigham and Women's Hospital (Boston, MA, United States)
California Institute of Technology (Pasadena, CA, United States)
Chang Gung University (Taoyuan City, Taiwan)
Children’s National Health System (Washington, D.C., United States)
Chongqing Medical University (Chongqing, China)
Cincinnati Children’s Hospital Medical Center (Cincinnati, OH, United States)
Deutsches Krebsforschungszentrum (Heidelberg, Germany)
Georgia Institute of Technology (Atlanta, GA, United States)
Inserm LabTAU (Lyon, France)
Institute of Cancer Research (Sutton, United Kingdom)
King's College Hospital (London, England)
Korea Institute of Science and Technology (Seoul, South Korea)
MD Anderson Cancer Center (Houston, TX, United States)
Medisch Centrum Nijmegen (Nijmegen, Netherlands)
Montefiore Medical Center (New York, NY, United States)
National Institutes of Health (Bethesda, MD, United States)
National Taiwan University (Taipei City, Taiwan)
Oklahoma State University (Stillwater, OK, United States)
Queen Mary Hospital of the University of Hong Kong (Pok Fu Lam, Hong Kong)
Roswell Park Cancer Institute (Buffalo, NY, United States)
San Diego State University (San Diego, CA, United States)
Seoul National University Hospital (Seoul, South Korea)
Stanford University School of Medicine (Stanford, CA, United States)
Sunnybrook Health Sciences Centre (Toronto, Ont., Canada)
Tulane University (New Orleans, LA, United States)
Universitätsklinik Köln (Cologne, Germany)
University of California, San Diego School of Medicine (San Diego, CA, United States)
University of Maryland School of Medicine (Baltimore, MD, United States)
Research Sites

Preclinical (Cont.)

University of Michigan (Ann Arbor, MI, United States)
University of North Carolina at Chapel Hill (Chapel Hill, NC, United States)
University of Southern California, Keck Hospital (Los Angeles, CA, United States)
University of Virginia Health System (Charlottesville, VA, United States)
University of Washington (Seattle, WA, United States)
Vanderbilt University (Nashville, TN, United States)
Virginia Polytechnic Institute and State University (Blacksburg, VA, United States)
Virginia-Maryland College of Veterinary Medicine (Blacksburg, VA, United States)
Wake Forest University Baptist Medical Center (Winston-Salem, NC, United States)
Washington University in St. Louis (St. Louis, MO, United States)

Clinical

Hôpitaux Universitaires Pitié-Salpêtrière (Paris, France)
Hospices Civils de Lyon (Lyon, France)
Stanford University (Stanford, CA, United States)
Universitatsklinik Köln (Cologne, Germany)
University of California, San Francisco (San Francisco, CA, United States)
University of Oxford (Oxford, England)
University of Virginia (Charlottesville, VA, United States)

Manufacturers

CarThera | Paris, France, www.carthera.eu
EDAP TMS | Lyon, France, www.edap-tms.com
INSIGHTEC LTD | Tirat Carmel, Israel, www.insightec.com
Profound Medical Corp | Mississauga, Canada, profoundmedical.com
SonaCare Medical | Charlotte, North Carolina, sonacaremedical.com
Theraclion | Malakoff, France, www.theraclion.com
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The “Goldilocks” Principle for Curing Brain Cancer
University of Minnesota News - October 2019

“Impressively, immunotherapy works only when the ultrasound is adjusted to maintain a stable body temperature as the cancer cells are ruptured.” – Clark Chen, Lyle French Chair in Neurosurgery and Head of the Department of Neurosurgery at the University of Minnesota Medical School

The Future of Focused Ultrasound: Movement Disorders and Beyond
Neurology Live - August 2019

“In Alzheimer disease models, FUS has been shown to activate microglia and increase phagocytosis of amyloid-β deposits in the brain by microglia and astrocytes.”

Foundation and Cancer Research Institute Host Workshop to Outline Future of Focused Ultrasound + Cancer Immunotherapy
FUSF website - July 2019

“There has been tremendous progress over the past few years demonstrating focused ultrasound’s ability to elicit an anti-tumor immune response, particularly in combination with immunotherapies,” said Jessica Foley, Focused Ultrasound Foundation’s Chief Scientific Officer.

The Second Coming of Ultrasound
Wired - January 2018

“Even more intriguing though, is the possibility of using ultrasound to remotely control genetically-engineered cells.”
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Key Publications


