



# Focused Ultrasound and Immunotherapy Summit

## Workshop Summary

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## Workshop Summary

### Focused Ultrasound and Immunotherapy Summit

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## Introduction

Focused ultrasound (FUS) 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 cancer. This novel technology focuses beams of ultrasound precisely and accurately on targets deep in the body without damaging surrounding normal tissue. Where the beams converge, the ultrasound produces a variety of therapeutic effects including thermal ablation, mechanical disruption of tissue, enhanced drug delivery, and induction of an anti-tumor immune response.

The field of cancer immunotherapy is progressing rapidly with several new agents approved by the FDA just this year. The most well-known are so-called checkpoint inhibitors that “take the brakes off” the immune response and enable a stronger immune attack against cancerous tumors throughout the body. Despite demonstrating tumor regression and increased overall survival, these therapies are effective in only 20-40% of patients. The efficacy of checkpoint inhibitors is improved in patients with an enhanced baseline anti-tumor immune response prior to treatment. This baseline response could potentially be elicited by radiation or other ablative therapies.

Ablative therapies—radiation, radiofrequency, cryoablation, laser, and focused ultrasound—have been shown to stimulate an immune response in preclinical and clinical studies. In addition, therapies such as radiation have demonstrated success when used in combination with immunotherapy, by providing the initial immune response that immunotherapy can then enhance.

In early 2015, the Focused Ultrasound Foundation (FUSF) and the Cancer Research Institute (CRI) held a workshop to discuss the potential use of FUS and immunotherapy for treating cancer. Several projects have been initiated since then to address many of the gaps in knowledge identified at the 2015 workshop. In June 2016, a multi-site consortium project was organized to assess the role of different FUS parameters in inducing an anti-tumor immune response in glioblastoma (GBM). The goal of the consortium is to use a standardized preclinical model at multiple research sites to study different FUS modalities for the treatment of GBM. This and other projects will help address some of the major questions. However, there are still many questions to answer in order to fully understand the potential for FUS immunomodulation in cancer therapy, including:

- What are the optimal sonication parameters? Are there instances where one is preferred over the others?
- For future preclinical research, which animal models and tumor models are best?
- What is the optimal timing of FUS and immunotherapy delivery?
- For combination therapies, what combinations should be considered?
- Ideal first clinical target for translation?
- Metrics to predict clinical success (CD8/Treg ratio, etc.)?
- Are there any FUS technology limitations that need to be addressed for translation?

On October 14, 2016, FUSF and CRI partnered again to convene a one-day meeting of scientists and clinicians to address the above questions related to focused ultrasound in combination with immunotherapy for oncology applications. The group discussed the status of and future directions for focused ultrasound research as it relates to cancer immunotherapy. There were presentations on the state of the field, relevant treatment mechanisms, and future directions for using FUS and immunotherapy. The workshop was also intended to foster collaboration by bringing together a multidisciplinary group of thought leaders including focused ultrasound experts, oncologists, surgeons, radiation oncologists, immunologists, and representatives from FDA, NIH, and industry.



## Background

Cancer cells develop throughout our lives, and the number of cancer cells in our body correlates with age, genetics, and environmental exposure (mutational load). However, the immune system provides constant monitoring and elimination of cancer cells from the body through a process called active surveillance. Cancerous cells with a higher mutational burden are typically more immunogenic, and therefore more likely to be recognized by the immune system. However, cancer cells may also develop defense mechanisms against immune cells. The most common defense is upregulation of checkpoint proteins, which protect the cancer cell by deactivating attacking immune cells. Several immunotherapeutics have been developed to help overcome this defense, the most well-developed of which are drugs targeting and blocking the programmed death receptor pathway (programmed cell death protein 1 (PD-1) and PD-L1 inhibitors).<sup>8</sup> These therapies—checkpoint inhibitors—‘release the brakes’ on the immune system and allow increased endogenous anti-tumor immune responses. These agents have demonstrated success in several different types of cancer, but only a small percentage of patients respond to therapy since they rely on a healthy population of anti-tumor immune cells to achieve a therapeutic effect.<sup>8</sup>

In addition to immunotherapy, which acts systemically, there are several focal therapies for the treatment of cancer including FUS, cryoablation, and radiation.<sup>9</sup> These therapies can provide non-invasive alternatives to surgery, and can lower morbidity, preserve normal parenchyma, and allow intraprocedural monitoring. Occasionally the entire tumor mass cannot be treated and some cancerous tissue remains. This can lead to an increased risk of recurrence in select patients. However, in other patients, treatment with these focal therapies has been shown to activate an anti-tumor immune response. Antigens from the remaining cancerous tissue are taken up by antigen-presenting cells (APCs) which then activate cytotoxic immune cells. This can lead to an abscopal effect in which treatment of the primary tumor also has an effect on metastases. However, focal therapy alone typically does not result in a sufficient systemic immune response to produce complete remission. It has been hypothesized that the anti-tumor immune response activated by focal therapies could be further enhanced by checkpoint inhibitors, producing a powerful synergy that increases both the efficacy of the focal therapy and the percentage of patients who respond to checkpoint blockade.

Currently, most studies combining focal therapies with immunotherapeutics utilize cryoablation. However, the RadVax trial investigated the abscopal effect in patients treated with a combination of radiation therapy and checkpoint blockade, demonstrating impressive efficacy.<sup>10</sup> At present, combination therapies utilizing FUS are early stage, but preclinical results are promising.

Clinical and preclinical evidence suggests that FUS, like traditional ablative therapies, may have effects on the immune system. For example, in some patients with metastatic pancreatic cancer, FUS treatment of the primary tumor induced an immune response against distant metastatic tumors outside of the FUS treated area (i.e. abscopal effect)<sup>1</sup>. Additional preclinical and clinical studies have shown that FUS treatment can enhance the immune response through increases in cytotoxic T cell activity,<sup>2</sup> dendritic cell activation,<sup>3,4</sup> heat shock protein and ATP up-regulation,<sup>5,6</sup> and circulating helper T cell lymphocytes.<sup>7</sup> The immune response produced by focused ultrasound could potentially be further enhanced by combination with immunotherapy. Given focused ultrasound’s non-invasiveness, use of non-ionizing radiation, and ability for conformal and precise ablation with no dose limitations, focused ultrasound could be more appealing for this combination therapy than other ablative modalities. Additionally, focused ultrasound can be used to increase the delivery of immunotherapeutics through better penetration into the target tumors.

## Workshop Presentations

Several brief presentations provided an overview of ongoing research using FUS to induce an anti-tumor immune response.

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**Stephen Hunt** from the University of Pennsylvania discussed anti-vascular ultrasound (AVUS) as a method to induce anti-cancer immunity. AVUS translates sound energy (ultrasound waves) into mechanical energy (vibration of microbubbles) generating frictional heating, shear forces, and cavitation. The resulting damage to the tumor vasculature causes hemorrhagic necrosis, vascular thrombosis, and inflammation. Mouse experiments (BL6 mouse with subcutaneous Hepa1-6 tumors) demonstrated that AVUS disrupts tumor perfusion and augments the enhanced permeability and retention (EPR) effect. Infiltration of CD45+/CD3+ immune cells was observed 24 hours post-treatment. Ten days after AVUS treatment, there were increases in tumor infiltrating B cells and cytotoxic T cells, and decreases in regulatory cells such as monocytes and T<sub>reg</sub> cells.

The researchers used a bilateral tumor model to examine the abscopal effect, examining the growth of the contralateral flank tumor following AVUS suppression of the primary tumor in combination with a PD-1 inhibitor. AVUS was very effective in controlling growth of the treated tumor, but PD-1 did not have an additive effect on the primary tumor. However, AVUS + PD-1 slowed the growth of the contralateral tumor and the combination was necessary to produce tumor regression. In closing, Hunt stressed the importance of the model chosen for studying the immune response, and that orthotopic models do not always support xenograft results. During the discussion, a question was posed about the vasculature of the tumor used in these models; Hunt replied that they did not investigate this closely. There was also a question about cytokine levels in the blood after AVUS in this model. Basic cytokine analysis in the mouse blood demonstrated increased circulating levels of IL-12 and IL-2.

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**Timothy Bullock** from the University of Virginia discussed the potential use of FUS and microbubbles to augment the immunogenicity of melanoma brain metastases, including early results in a mouse model. Some patients with melanoma demonstrate good clinical success after immunotherapy, but treatment of melanoma brain metastases has shown very little efficacy to date. Furthermore, the percentage of melanoma patients who respond to immunotherapy is only 10-20%, and the response depends on the level of immune cell infiltration within the tumor. The purpose of using FUS for the treatment of metastatic melanoma is to promote immune recognition of 'cold' brain metastases, inducing immune cell infiltration and increasing the likelihood that the patient will respond to checkpoint blockade. Preclinical results have shown that FUS can enhance access of antibodies to tumors and tumor-infiltrating lymphocytes, augment natural killer (NK) and T cell recruitment and extravasation and increase the function of effector cells at the tumor site. Possible mechanisms for ultrasound-mediated immunomodulation include endothelial cell activation, microvascular disruption, and tumor tissue disruption.<sup>11</sup> The B16cOVA mouse melanoma line was injected intracranially to investigate the role of FUS-mediated blood brain barrier (BBB) opening in inducing an anti-tumor immune response, but the response was poor. They also found that brain metastases are dominated by myeloid cells and microglia, which are of

unknown immunological significance. There was also no evidence of tumor-specific CD8+ T cells in the tumor or tumor-draining lymph nodes. Bullock plans to study whether activated tumor-specific T cells can access brain metastases, and whether intratumoral tumor-infiltrating lymphocytes (TILs) are exposed to increased immunomodulatory antibodies after FUS treatment. Following the presentation there was a discussion about characterizing the acute immune response to FUS, and well-designed studies are needed to answer this important question.

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**Chandan Guha** from Albert Einstein College of Medicine discussed low-intensity focused ultrasound (LOFU) for the reversal of T cell tolerance. Project ENERGY.01 at the Einstein Institute of Onco-Physics aims to explore ablative technologies for immune-priming. Various focal energy-based therapies such as radiotherapy, LOFU, and microwave can ‘prime’ the immune system, potentially enhancing the efficacy of immunotherapies such as immune checkpoint inhibitors and T cell agonists. Radiation therapy in combination with Flt-3 ligand (GM-CSF) prolonged overall survival in a mouse model of metastatic lung cancer.<sup>12</sup> These results inspired further explorations with other energy-based modalities.

In the B16 mouse model of melanoma, treatment of the primary tumor using LOFU (non-ablative ultrasound) can reverse T cell anergy and activate dendritic cells in the tumor and tumor-draining lymph node. Translocation of surface calreticulin and activation of heat shock proteins (HSPs) were identified as potential mechanisms for the LOFU-induced immune response. LOFU was also shown to activate cell-surface receptors on the endoplasmic reticulum, and was used as an adjuvant to potentiate the effects of radiotherapy and improve control of distant metastases.<sup>13</sup> During the discussion, a question was asked regarding the difference between LOFU and cryoablation. Guha explained that cryoablation is thermal and designed to ablate the tumor. In contrast, LOFU is mechanical and stresses but doesn’t kill tumor cells, causing them to upregulate expression of various stress-induced antigens to promote immune recognition of the tumor. There was also a question about how this could translate to the clinic, and how much of the tumor needs to be treated. Guha stated that there is no evidence yet, but it is likely that the full tumor would need to be treated with LOFU. Partial treatments would likely allow compensation by the tumor stroma.

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**Petros Mouratidis** from the Institute of Cancer Research (UK) presented on the biological and immunological effects of thermal therapies. Therapeutic ultrasound in combination with immunotherapy may provide treatment approaches that can overcome cancer cells’ genetic heterogeneity. In vitro experiments were carried out in colon cancer cells (HCT116) treated with thermal exposure at different temperatures. Results suggested activation of immunogenic cell death produced by increased calreticulin on the cell surface, increased ATP secretion, and reduced exposure of CD47 on the cell surface. HCT116 cells are considered immunologically ‘hot,’ so these experiments were also carried out in an immunologically ‘cold’ cancer model (pancreatic Panc02 cells). Some increases in calreticulin were still observed. An in vivo study is underway to look at the effects of HIFU in combination with checkpoint inhibitors. There remain several questions to investigate for translation to cancer patients including standardization of therapeutic ultrasound parameters (mild heating vs. thermal ablation) and understanding the best tumor model to study these effects (hot vs. cold).

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**Katherine Ferrara** from the University of California, Davis discussed the combination of focal therapies with immunotherapy to treat cancer. Preclinical experiments (in vitro and in vivo) show that mechanical disruption with HIFU can release tumor antigens. Additionally, LOFU with microbubbles can disrupt cell membranes and the vasculature.<sup>14</sup> To date, thermal effects have demonstrated greater response in preclinical breast cancer models, with partial HIFU tumor ablation plus chemotherapy resulting in a complete and durable response.<sup>15</sup> Temperature-sensitive liposomes (TSLs) containing chemotherapeutics were combined with thermal ultrasound to produce a complete response in additional preclinical studies.<sup>16</sup> Further studies demonstrated that the combination of immune stimulation with CpG and ultrasound-mediated delivery and activation of TSLs resulted in a complete local response and produced an abscopal effect, reducing systemic tumor growth.<sup>17</sup> Thermal ablation plus CpG and a checkpoint inhibitor diminished the abscopal effect and did not improve survival. However, altering the time course of the therapy was able to reverse this negative synergy. Utilizing a priming protocol rather than concurrent therapy, they achieved a complete response. Protocols combining thermal therapy with immunotherapy require optimization to move forward into larger preclinical models and eventually patients. During the discussion, a question was asked on whether models that were immunogenic would need immune stimulation. Ferrara stated that this scenario is probable based on the results that they have seen to date.

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**Timothy Bullock** also spoke about the GBM Immunotherapy Consortium, which was formed to compare the immunotherapeutic effects of different ultrasound modes in a mouse model of GBM. The standard of care for GBM, surgery plus radiotherapy and temozolomide, produces a 5-year survival rate of only 12%. Recent research has demonstrated that the brain is not immunoprivileged, and immune cells travel in and out of the brain through meningeal lymphatics, raising hope that immunotherapies may be efficacious against GBM. However, GBMs are considered immunologically ‘cold’, with poor infiltration of immune cells. There are several questions about the use of FUS as an adjunct to immunotherapy that need coordinated approaches to answer:

- Are there discrete differences in the ability of FUS modalities to induce immunogenic cell death?
- Is antigen release equivalent between FUS approaches?
- Amount and form
- Duration
- Access to dendritic cells
- How does FUS influence the expression of checkpoint ligands in the tumor microenvironment?
- What other mechanisms of adaptive resistance are present in GBM and are targetable or induced by different FUS modalities?

The GBM consortium will use the same GBM model (intracranial GL261luc2 cells in C57bl/6 mice) to examine these questions using several different modes of FUS, each performed at a different site. These modes include: ablation, hyperthermia, histotripsy, and pulsed FUS/LOFU. Immune cell infiltration will be assessed via standardized immunohistochemistry and flow cytometry protocols. The goals of the consortium are to define an approach that optimally increases CD8:Treg ratio, identify the most functional CD4, CD8, and NK cells in the tumor microenvironment, and control of tumor outgrowth. The outcome of these experiments will help to develop a baseline understanding of the immune response to different modalities.



## Overall Discussion and Evidence Gaps

The discussion focused on ideas for a framework to advance the use of FUS in combination with immunotherapy for the treatment of cancer.

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### Recommendations and considerations for additional multisite consortium projects (similar to GBM Immunotherapy Consortium)

#### Experimental Design Considerations

Select immunotherapy agents that are already FDA approved

- Clinical combination trials with unapproved drugs and/or devices from different companies would be very difficult to carry out
- PD-1/PD-L1 inhibitors can produce both negative and positive synergy with FUS—timing of immunotherapeutic administration is important

Work backwards from the clinical situation to identify areas of research where there is a critical unmet need for patients (e.g. pancreas, brain) or where there is interest from industry (e.g. prostate or kidney)

- Define endpoints that will prove efficacy
- Add a standard of care control group to allow comparisons between various treatment options
- Mouse models are useful for determining dose and timing, but may not predict the clinical situation

#### Experimental Model Suggestions

Pancreatic Cancer

- Existing mouse model (KPC mice or other orthotopic models)
- Accurately represents the human clinical situation
- Existing knowledge of the role of the immune system in pancreatic cancer
- Orthotopic models difficult to access with FUS

Melanoma Cancer

- Excellent existing mouse models (B16 and B16 Ova)
- Expresses checkpoint antigens
- Immune response well characterized

Breast Cancer

- Existing mouse model
- Expresses checkpoint antigens
- Already clinically treated with FUS (benign and malignant tumors)

Prostate Cancer

- Existing mouse model
- Already clinically treated with FUS

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### **Is there a biomarker or assay that could be used in ongoing FUS trials throughout the world? The Foundation is interested in gathering information on the immune response in current FUS clinical trials.**

First determine the immunological effects of FUS and then identify a secondary immune monitoring marker

- Measuring levels of PD-1 following treatment with a PD-L1 inhibitor is currently used in the clinic to predict response to PD-1 treatment

Imaging biomarkers may provide useful both in preclinical and clinical applications

- PET is already in use for some clinical trials

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### **What drug targets (i.e. PD-1 and CTLA-4) makes the most sense for use with FUS?**

Consider additional checkpoint regulatory molecules such as LAG3 or TIM-3

Optimal treatment time course is still not well understood

- Must first understand when these molecules are important in the immune response

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### **To answer the big questions that remain, what is the next project that should be started?**

#### **Preclinical Project Ideas**

Determine the FUS mechanism of action in cancer and whether it changes the mutagenicity of the tumor (antigenic load) or stimulates the immune system

- Can FUS convert immunogenically ‘cold’ tumors to ‘hot’?

Determine whether FUS affects tumor cells or the tumor microenvironment

Develop an assay panel/calibration point for use in comparing FUS modalities

- T cells activity/infiltration
- Radiation field has identified standards for immune responses

#### **Clinical Project Ideas**

Develop patient registries to track potential immunological effects of FUS treatment

Prostate Cancer: monitor metastasis markers after combination treatment (HIFU + immunotherapy)

Kidney Cancer: combination HIFU + immunotherapy for patients with metastatic disease

- Survival advantage for nephrectomy is 6 months and 1 year for immunotherapy

Breast Cancer and/or Melanoma: large disease burden and accessible to FUS

- Lung and pancreas would be difficult FUS targets

#### **Other Considerations**

Focus on FUS modalities that could rapidly transition to patients

- Most clinically available FUS systems are capable of ablation, hyperthermia, and LOFU; histotripsy may not be available yet in most systems

For collaborations with the pharmaceutical industry, it will be necessary to have data showing that FUS affects a specific and measurable target

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### **Passive cavitation is detectable with clinical FUS units, is it possible to standardize the LOFU methods with microbubbles?**

Possible with monitoring of vibrations or broadband emissions

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### **Any other ideas or projects that haven't been mentioned?**

Compare cryotherapy to FUS to see which modality is better for the patient

Need to standardize FUS treatments across devices and modalities

- Heat (HIFU, mild hyperthermia) and cavitation (LOFU, AVUS, histotripsy)
- Develop and encourage use of standardized parameter reporting in literature

Develop a repository for clinical data

- Characterization/parameters for each commercial FUS system to permit easier comparison across sites and manufacturers

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### **Is there a need for large animal models?**

Yes, particularly for abdominal targets

- Currently no large animal model for pancreatic cancer
- Pig model for hepatocellular carcinoma (HCC)
- Woodchuck model for HCC currently in development for use in MR and HIFU experiments

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## Outcomes and Next Steps

Key takeaways from the meeting included a need to better understand the importance of timing with respect to combinations of FUS and immunotherapeutics and design preclinical trials within the context of what is feasible in the clinic. The FUS Foundation will continue engagement with this community to move the research forward. Participants were encouraged to reach out to the Foundation with any research ideas or project proposals in this area. In addition, the Foundation identified several action items to further enable this effort:

### **Action Items**

- Develop reporting standards for FUS parameters for preclinical/clinical FUS experiments to permit standardization across experiments
- Develop repository for characterization data of clinical systems to permit standardization across systems
- Support preclinical and clinical studies assessing FUS in combination with immunotherapeutics for the treatment of cancer

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## Abbreviations

<b>APC</b>	Antigen-presenting cells	<b>HIFU</b>	High-intensity focused ultrasound
<b>AVUS</b>	Anti-vascular ultrasound	<b>HSP</b>	Heat shock proteins
<b>BBB</b>	Blood brain barrier	<b>LOFU</b>	Low-intensity focused ultrasound
<b>EPR</b>	Enhanced permeability and retention effect	<b>NK</b>	Natural killer cell
<b>FDA</b>	U.S. Food and Drug Administration	<b>TIL</b>	Tumor-infiltrating T-lymphocytes
<b>FUS</b>	Focused ultrasound	<b>TSL</b>	Temperature-sensitive liposomes
<b>GBM</b>	Glioblastoma multiform		

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