

## Focused ultrasound-enhanced cell therapy for brain tumors: Summary of roundtable discussions

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### Abstract

Cell-based immunotherapies have emerged as promising strategies for brain tumors, offering the potential for targeted and durable antitumor responses. However, their efficacy has been limited by challenges unique to the central nervous system, including suboptimal delivery routes and an immunosuppressive tumor microenvironment that impairs cell function. Focused ultrasound (FUS) is a noninvasive technology that, when combined with intravenously administered microbubbles, can transiently and reversibly increase blood-brain barrier permeability. FUS has improved drug delivery to brain tumors in clinical trials and offers compelling opportunities to enhance trafficking, activation, and control of therapeutic cells. Despite this potential, critical questions remain regarding the timing and sequencing of FUS with cell therapies, the impact of FUS on the tumor and neuroimmune microenvironments, strategies to mitigate acute and delayed toxicities, and methods to tune potency to maximize tumor specificity while minimizing bystander tissue injury. To address these challenges, the Focused Ultrasound Foundation convened a multidisciplinary roundtable in March 2025. Experts in neuro-oncology, neuroimmunology, cell therapy, neurosurgery, and FUS participated. Discussions focused on cell delivery routes, pharmacokinetics and blood-brain barrier opening, tumor microenvironment and CNS inflammation, FUS-induced immune modulation, clinical trial design, and approaches to safety monitoring and cell control. In this review, we summarize the discussions and key messages from the roundtable, which may serve as a foundation for advancing FUS-enhanced cell therapy for brain tumors in a collaborative manner.

### Key Points

- Focused ultrasound enables enhanced cell delivery to brain tumors through blood-brain barrier modulation
- Focused ultrasound induces immune activation, and allows precise control of engineered cells' activities
- Critical knowledge gaps include optimal timing, delivery route for cellular therapies, inflammatory thresholds, and mechanisms of immune modulation
- Progress requires innovative trial designs, expanded tissue access, and consortium-based approaches

Cell-based immunotherapies have emerged as promising strategies for treating brain tumors, with multiple approaches under investigation, including tumor antigen-specific T cells, chimeric antigen receptor (CAR) T cells, natural killer (NK) cells, and NKT cells. These therapies offer the potential for targeted, durable antitumor responses; however, their efficacy in brain tumors has been limited by several unique challenges inherent to the

central nervous system (CNS). Chief among these is the blood-brain barrier (BBB), which restricts the trafficking of therapeutic cells to tumor sites, and the immunosuppressive tumor microenvironment that impairs cell function upon arrival.

Focused ultrasound (FUS) is a noninvasive technology that can transiently and reversibly open the BBB when combined with intravenously administered microbubbles. FUS has been

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shown to safely improve the efficiency of drug delivery to the brain in clinical trials for glioblastoma.<sup>1</sup> This BBB opening (BBBo) is temporary, focal, and can be repeated, offering precise spatiotemporal control over therapeutic delivery. Beyond passive delivery enhancement, emerging evidence suggests that FUS may actively modulate the tumor immune microenvironment through sterile inflammation, cytokine release, and altered immune cell trafficking patterns.<sup>1-5</sup>

The convergence of cell therapy and FUS presents both opportunities and complexities. While the potential for synergy is clear, beyond delivery challenges, the timing of such combinations, their impact on the tumor microenvironment, strategies to mitigate toxicity, and methods to control the potency of the approach to ensure tumor specificity while avoiding bystander cell and organ toxicity remain to be optimized.

On March 27, 2025, the Focused Ultrasound Foundation convened experts in neuro-oncology, neuroimmunology, cell therapy, and FUS to address these challenges systematically. This report synthesizes the discussions and identifies priorities for advancing FUS-enhanced cell therapy toward clinical translation.

## Challenges in Cell Therapy for Brain Tumors

### *Neuroimmunology and Cell Therapies*

The current understanding of the neuroimmune system encompasses antibody-mediated, cellular, and innate mechanisms. Although the CNS presents unique immune challenges, T cells are clearly active and relevant in the brain, with perivascular and meningeal macrophages, microglia, and sometimes dendritic cells serving as antigen-presenting cells (APCs).<sup>6</sup> T cells must be primed in the periphery and are then restimulated upon entering the CNS.

In this context, FUS-enhanced blood-brain barrier opening (BBBo) may offer a physiological route of entry for immune cells, enabling perivascular engagement and mimicking natural immune effector responses. Compared to intracavitary or intraventricular (ICV) approaches, this method offers a more targeted and tunable delivery option, thereby better preserving physiological trafficking.

Experience from CART-cell therapy for brain tumors, such as diffuse intrinsic pontine glioma (DIPG), illustrates that intravenous administration can fail to elicit a strong response, whereas ICV delivery can produce more robust activity—underscoring the extent to which the roles of both the tumor microenvironment and the delivery route in modulating therapeutic efficacy<sup>78</sup> remain to be understood.

From a manufacturing standpoint, CART-cell design can also be optimized for improved safety and efficacy. These include logic-gated, multitargeting, armored, and on/off switchable platforms.<sup>9</sup> There are trade-offs between autologous, allogeneic, and in situ strategies: allogeneic or in situ approaches may offer improved manufacturability and scalability but introduce new challenges related to graft rejection and immune toxicity.<sup>79</sup> Given the current financial environment for biotech, scalable and cost-effective approaches are critical.<sup>10</sup>

## Key Points

- The CNS is immunologically active: T cells, microglia, and perivascular APCs provide a substrate for effective cell therapy if appropriately engaged.
- FUS-enhanced BBBo offers a physiologic, tunable route to perivascular entry that may complement or, in some settings, rival intracavitary/ICV delivery.
- CART engineering and sourcing (autologous vs. allogeneic vs. in situ) must balance manufacturability, cost, and immune toxicity, especially in the current financial climate.

### *CNS Inflammation and Lymphocytes*

T-cell dynamics in the CNS after infection illustrate how effector cells and resident populations can shape neuroinflammation. CD8<sup>+</sup> T cells can persist in the brain post-infection and activate microglia, contributing to synapse elimination via complement signaling.<sup>11-13</sup> However, not all infiltrating lymphocytes become resident memory T cells (TRMs). TRM formation appears dependent on local cytokines, such as TGF- $\beta$ , and chemokines, including CXCL16, which maintains TRMs in the CNS, and CCL2, which limits their activation.

Within this framework, CCR2<sup>+</sup>TRMs may play a protective role by limiting the neurotoxic effects of systemic cytokines.<sup>14</sup> These insights have direct implications for the timing of apheresis and product manufacturing in cell therapy. To maximize the quality of the T-cell pool and potentially reduce susceptibility to systemic cytokine-driven neurotoxicity, apheresis is best timed post-surgery and before adjuvant therapies, when peripheral T cells are healthier and less depleted.

More broadly, the TRM and chemokine milieu offers potential levers to modulate CNS inflammation in patients receiving cell therapies and FUS, either by preserving protective TRM functions or limiting maladaptive microglial activation and synapse loss.

## Key Points

- Persistent CD8<sup>+</sup> T cells and TRMs shape CNS inflammation and synaptic integrity via microglia and complement pathways.
- TRM differentiation depends on local cytokine and chemokine cues that may be modified by therapy and disease state.
- CCR2<sup>+</sup> TRMs may protect against systemic cytokine-induced cognitive toxicity, highlighting the need to monitor and modulate systemic inflammation.
- For autologous products, apheresis should be timed after surgery but before adjuvant therapy to capture the healthiest possible T-cell compartment.

### Clinical Trial Design Considerations

Clinical trial design for cell therapies in brain tumors must integrate delivery route, tumor biology, and immune context to demonstrate that the product reaches the tumor and exerts the intended effect. A central challenge is identifying effective delivery routes—intravenous, ICV, intratumoral, or intracavitary—based on tumor characteristics, patient-specific factors, and immunologic context.<sup>15,16</sup> Delivery strategies should be chosen based on tumor characteristics (e.g., diffuse vs. bulky disease), anatomical compartmentalization, and the specific mechanism of action of the cell product.

Early-phase trials are especially critical and should be designed to demonstrate tumor access. Window-of-opportunity or neoadjuvant designs can confirm that cell delivery by any route (IV, IC, IT, etc.) leads to therapeutic cell accumulation and biodistribution throughout the tumor. In this setting, FUS-BBBo can be evaluated as an adjunct to systemic delivery when perivascular access and spatial targeting are advantageous.

Preclinical FUS studies indicate that simultaneous administration of cell-based immunotherapy and FUS sonication leads to the highest brain deposition, whereas delayed or prior delivery relative to sonication results in significantly fewer cells reaching the CNS.<sup>2</sup> These findings reinforce the concept of FUS-BBBo as a time-locked “entry window” for circulating effector cells that needs to be explicitly integrated into delivery strategies and trial design.

These preclinical findings, together with clinical experience showing that intratumoral and intrathecal routes can be advantageous for bulky or compartmentalized disease, support a pragmatic, tumor-specific approach to route selection rather than a “one-size-fits-all” paradigm.

Combining novel cell therapies with medical devices such as FUS introduces additional regulatory complexity. Early-phase trials must strike a balance between innovation and patient safety, given the risks of neuroinflammation and edema. Recent CNS CAR T-cell trials have encountered tumor inflammation–associated neurotoxicity (TIAN). The Monje et al.<sup>8</sup> study of GD2-CAR T cells in H3K27M-mutated DIPG highlighted reversible toxicity and intracranial pressure management with supportive care, including CSF drainage, IL-6R blockade (tocilizumab), and IL-1R blockade (anakinra). FUS may reduce systemic cytokine release by localizing delivery, but prospective data are needed.

There is a strong consensus on the need for preclinical models that faithfully reproduce CNS immune responses and glioma biology. Correlates such as CSF cytokine levels, T-cell persistence, and radiographic markers of edema can be proposed as surrogate endpoints for early trials.<sup>15</sup> Extensive preclinical validation and integration of translational biomarkers into trial designs will be essential to satisfy both scientific and regulatory requirements.

### Key Points

- Route of delivery (IV, ICV, intratumoral, intracavitary) must be individualized based on tumor anatomy, compartmentalization, and immune contexture, with FUS-BBBo offering an additional tunable option.
- Early “window-of-opportunity” or neoadjuvant trials are essential to directly demonstrate tumor targeting, biodistribution, and pharmacodynamic effects of cell therapies.
- Preclinical data suggest that synchronizing FUS sonication with cell infusion is likely critical to maximize CNS deposition and should be built into future protocols.
- Safety planning must explicitly anticipate TIAN and edema, with predefined algorithms for ICP monitoring, CSF drainage, and cytokine blockade, particularly when combining cell therapies with FUS.
- Robust preclinical models and translational biomarkers (e.g., CSF cytokines, T-cell persistence, imaging markers of edema) are needed as surrogate endpoints to guide dose, schedule, and route selection in early-phase trials.

## Role of Focused Ultrasound in Cell Therapy for Brain Tumors

### Pharmacokinetics and Immune Modulation of Ultrasound-Based Blood-Brain Barrier Opening in Humans

Human clinical data using the Carthera implantable ultrasound device for BBBo in glioblastoma patients have demonstrated enhanced penetration of paclitaxel into human brain tissue, a drug that ordinarily does not cross the BBB.<sup>1</sup> An examination of the timing of BBB closure following FUS revealed that most drug uptake occurs rapidly after low-intensity pulsed ultrasound with microbubbles (LIPU-MB), highlighting the need for precise coordination of therapeutic administration to benefit from an effective delivery window.<sup>1</sup> In humans, rapid restoration of BBB integrity after sonication can lead to trapping of drugs and biological agents in the brain, resulting in prolonged permanence.<sup>17</sup>

Beyond enhanced delivery, these clinical and preclinical observations suggest immunological consequences of BBBo, indicating that BBBo may act not only as a mechanical conduit for therapeutics but also as an immune modulator. A novel combinatorial strategy of FUS and doxorubicin appears to sensitize tumors to anti-PD-1 checkpoint inhibition in patients and in preclinical models,<sup>4</sup> with mechanistic

assessments indicating that doxorubicin plays a key role in enhancing expression of receptors critical for the mechanism of action of anti-CTLA4 immune checkpoint blockade, and ultimately, immune cell recruitment.<sup>4,18</sup>

To better understand how FUS reshapes the neurovascular interface, there are opportunities to systematically assess both local and systemic effects of FUS-mediated BBB using histological and molecular markers: (1) IgG extravasation to quantify spatial spread, (2) ICAM staining as a marker of endothelial activation throughout the vascular tree, (3) markers for BBB polarity of chemokines and transporters,<sup>19–21</sup> and (4) markers for pericytes and astrocytes to evaluate their role in maintaining or modulating BBB integrity and trafficking. These studies could provide essential mechanistic insight into how FUS-BBBo configures a permissive or restrictive environment for drug and cell entry.

### Key Points

- FUS-mediated BBBo can enable brain penetration of agents that are otherwise BBB-impermeant, with most uptake occurring within a narrow post-sonication window.
- Rapid BBB restoration can trap drugs and biologics in the brain, prolonging local exposure.
- BBBo is not purely mechanical; combinations such as FUS + doxorubicin can modulate expression of receptors critical for the mechanism of action of anti-CTLA4 immune checkpoint blockade, antigen presentation and immune cell recruitment, influencing response to checkpoint blockade.
- Spatially resolved biomarkers (IgG extravasation, ICAM, pericyte and astrocyte markers) are needed to map how FUS reshapes the neurovascular interface and informs dosing and timing.

### *Combination of Focused Ultrasound with Immunotherapy to Target CNS Malignancies*

FUS can be used to modulate the immunosuppressive brain tumor microenvironment, which otherwise hinders antigen drainage, T-cell priming, and activation, and thereby limits T-cell infiltration and persistence. To address immune escape by CAR-negative tumor cells, emerging strategies aim to activate endogenous immune responses.<sup>22</sup>

Within this framework, FUS may recondition the tumor microenvironment by altering cytokine gradients, promoting antigen presentation and spreading, and enhancing the efficacy of cell therapies by broadening the immune system's recognition of tumor targets. Combining FUS with adjuvants (e.g., cytokines, TLR ligands) can enhance immune priming and induce epitope spreading, which involves the priming of host-derived T cells that recognize multiple antigens not directly targeted by the immunotherapy itself. In a GBM mouse model with heterogeneous CAR antigen expression, FUS BBBo combined with CAR T cells and immune adjuvants significantly improved survival, whereas treatment with CART cells alone failed to improve survival

due to the outgrowth of tumor cells that did not express the CAR target antigen (Gallus et al. manuscript in preparation, 2025).

Discussion highlighted that different tumors may require distinct adjuvant strategies and that inflammation thresholds that are safe yet sufficient to trigger therapeutic immunity need to be defined. Preclinical data suggest that FUS alone may be insufficient to overcome the immunosuppressive brain tumor microenvironment, prompting consideration of rationally selected adjuvants to amplify or sustain immune activation. While no major safety concerns were noted with FUS itself, participants emphasized that the choice of adjuvant and dosing must be optimized to minimize excessive neuroinflammation. The complexity of tumor-specific immune modulation, coupled with safety concerns, also underscores the value of robust preclinical modeling and careful design of early-phase trials.

The role of myeloid cells emerged as a key consideration. These innate immune cells may exert both pro-inflammatory and immunosuppressive effects within the tumor microenvironment. Understanding how FUS and associated adjuvants influence myeloid cell recruitment, activation state, and spatial distribution could offer new avenues to tip the balance toward productive antitumor immunity.

This complexity underscores the value of robust preclinical modeling and careful design of early-phase trials to deconvolute the contributions of FUS, adjuvants, cell therapies, and myeloid populations.

### Key Points

- FUS can recondition the brain tumor microenvironment to enhance antigen presentation, T-cell priming, and epitope spreading beyond the initial CAR target.
- Combining FUS with immune adjuvants and cell therapies can overcome antigen heterogeneity, but tumor-specific adjuvant strategies and safe inflammation thresholds must be defined.
- Myeloid cells are central modulators of FUS-enhanced responses; strategies should explicitly assess and harness their protumor vs antitumor functions.
- Preclinical models that integrate FUS, adjuvants, and heterogeneous tumors are essential to design safe and effective early-phase combination trials.

### *Focused Ultrasound for the Control of Immune Cell Trafficking and Function*

Mechanistic modeling of microbubble dynamics has identified FUS parameter regimes that enhance wall shear stress and upregulate endothelial adhesion molecules capable of facilitating T-cell diapedesis across the BBB.<sup>5,23</sup> Experimentally, FUS can selectively upregulate P-selectin and ICAM and promote T-cell extravasation and localization in murine brain tumors,<sup>5</sup> demonstrating that FUS can be

used not only to open the BBB but also to actively steer immune cell trafficking at the neurovascular interface.

FUS-responsive genetic switches can also be integrated into CAR constructs to enable localized, metronomic, on-demand activation of therapeutic cells. In a HER2-positive brain metastasis model containing 20% HER2-negative cells to mimic antigen heterogeneity, FUS-controlled CART activation significantly improved survival and tumor control,<sup>24</sup> highlighting the potential of spatiotemporal control to address antigen heterogeneity and enhance therapeutic precision.

The versatility of FUS mechanisms—shaped by variables such as frequency, pressure, duty cycle, sonication pattern, timing of therapeutic delivery, and the prevailing immune context—offers broad therapeutic potential but creates a complex parameter space. Participants noted that reproducibility and comparability across studies will depend on standardized reporting of acoustic parameters and immunological readouts, including endothelial activation markers, patterns of immune cell trafficking, and functional outcomes. Collaborative frameworks, such as consortium-based or adaptive clinical trials, were highlighted as promising avenues for systematically exploring and optimizing FUS-based immune modulation.

A recurring theme was the balance between rigorous preclinical validation and the necessity of proceeding to clinical settings to obtain meaningful answers, given the inherent limitations of animal models in fully recapitulating the complexity of human neurovascular and immune systems.

## Key Points

- FUS parameters can be tuned to upregulate adhesion molecules and promote targeted T-cell extravasation into brain tumors.
- FUS-responsive genetic switches in CAR constructs enable spatially and temporally controlled cell activation, improving control of heterogeneous tumors.
- The complexity of FUS parameter space demands standardized reporting of acoustic settings and immune readouts, and will benefit from consortium or adaptive trial structures.
- Translation of FUS-controlled trafficking from mice to humans will require iterative, biomarker-rich early trials that explicitly test and refine model-derived predictions.

## Conclusions and Path Forward

This roundtable brought together investigators in neuro-immunology, brain tumor biology, cell engineering, and FUS to examine how FUS can realistically augment cell therapies for brain tumors. Across the discussions, a common view emerged: FUS is not a standalone modality, but a versatile platform that can (1) open and reconfigure the neurovascular interface, (2) modulate the tumor immune microenvironment, and (3) provide spatial and temporal control over therapeutic cells. To translate this potential into clinical impact, FUS must be systematically integrated with

cell engineering, rational route and timing of delivery, and biomarker-rich clinical trial designs.

### *A Roadmap for FUS-enhanced Cell Therapies in Brain Tumors*

Building on the insights from the discussions, we propose the following priorities to guide coordinated progress. This revolves around six issues that need to be addressed concurrently:

1. Define trafficking and pharmacodynamic benchmarks in humans: Early “window-of-opportunity” and neo-adjuvant trials should be designed explicitly to demonstrate tumor access, biodistribution, and pharmacodynamic effects of FUS-enhanced cell therapies, including paired tissue/CSF sampling from resection or biopsy, imaging of edema and perfusion, and longitudinal tracking of cell persistence.
2. Clarify FUS effects at the neurovascular interface using human tissue, including cadaveric sources: Systematic analyses of human and preclinical tissue—using markers of IgG extravasation, endothelial activation and pericyte/astrocyte responses—are needed to map how different FUS parameter regimes alter BBB and blood-tumor barrier integrity and guide drug and cell delivery windows. This should include expanded access to human brain tissue, including cadaveric samples, to interrogate FUS-induced changes at cellular and vascular resolution that cannot be fully captured in vivo.
3. Map immune modulation, including myeloid and TRM responses, and rational adjuvant use: Studies should dissect how FUS, alone and in combination with immune adjuvants, including cytokines, TLR ligands, oncolytic or chemotherapeutics, reshapes TRMs, myeloid cells, complement/microglia signaling, and epitope spreading in brain tumors, and how these changes correlate with therapeutic response versus neurotoxicity. A key goal is to tailor adjuvant strategies to tumor type and immune contexture, rather than assuming a single adjuvant regimen will be suitable across all CNS malignancies.
4. Establish safe inflammatory thresholds, adjuvant intensity, and management algorithms: Tumor- and regimen-specific “inflammatory windows” must be defined, using CSF cytokines, imaging markers of edema, and clinical endpoints. This includes determining the dose, schedule, and combination of adjuvants that achieve sufficient immune activation without excessive neurotoxicity. Early-phase protocols should embed predefined algorithms for TIAN and edema management, including intracranial pressure monitoring, CSF diversion, and targeted cytokine blockade.
5. Optimize and standardize FUS parameters and delivery routes: Comparative studies should evaluate IV, ICV, intratumoral, intracavitary, and FUS-BBBO approaches across cell products and tumor locations, with standardized reporting of acoustic parameters and immune readouts to enable reproducibility, cross-trial learning, and meta-analyses.

6. Leverage consortium-based and adaptive frameworks: Multicenter collaborations, with shared protocols, data standards, and correlative science, will be critical to explore the complex FUS parameter space efficiently, validate FUS-responsive cell constructs, and align with regulatory expectations for device-cell therapy combinations.

Together, these steps aim to move FUS-enhanced cell therapy beyond isolated proof-of-concept efforts toward a coordinated translational agenda, with clear benchmarks for success and shared tools for the neuro-oncology community.

## Keywords

brain tumor | cell therapy | focused ultrasound

## Author Contributions

F.P. drafted the manuscript, all authors revised and edited.

## Conflict of Interest Statement

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