

## Maximizing Local Access to Therapeutic Deliveries in Glioblastoma. Part IV: Image-Guided, Remote-Controlled Opening of the Blood–Brain Barrier for Systemic Brain Tumor Therapy

ANIRUDH SATTIRAJU<sup>1</sup> • YAO SUN<sup>1</sup> • KIRAN KUMAR SOLINGAPURAM SAI<sup>1</sup> • KING C.P. LI<sup>2</sup> • AKIVA MINTZ<sup>1</sup>

<sup>1</sup>Department of Radiology, Brain Tumor Center of Excellence, Wake Forest Baptist Medical Center Comprehensive Cancer Center, Winston Salem, NC, USA; <sup>2</sup>Carle Illinois College of Medicine, Urbana, IL, USA

**Author for correspondence:** Akiva Mintz, Department of Radiology, Columbia University Medical Center. Columbia University College of Physicians and Surgeons Radiology Administrative Office, 1st Floor, Room PH1-333 New York, NY 10032, USA. E-mail: am4754@cumc.columbia.edu

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**Abstract:** Disease in the central nervous system (CNS) is a challenge to treat with systemic therapies due to the presence of the blood–brain barrier (BBB), which excludes common and novel therapeutics. For example, glioblastoma (GBM) is the most common and aggressive primary brain tumor, with an extremely poor prognosis due to infiltrating tumor cells in areas of normal brain. A primary

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challenge of treating this devastating disease is the exclusion of systemic therapies from the CNS. While efforts are being made to develop strategies for designing drugs that can pass through the BBB, there are also efforts to use novel engineering techniques to safely allow any systemic therapy into the CNS and areas of disease. In this chapter, we focus on using high-intensity focused ultrasound (HIFU) to circumvent the BBB.

**Key words:** Blood–brain barrier; Glioblastoma; High-intensity ultrasound; Stem cells

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## Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor, with an extremely poor prognosis (1). The dismal prognosis is a direct result of the fact that standard therapies fail to eradicate residual or infiltrating cells that reside adjacent to and infiltrate normal brain tissue. This failure is mostly due to the unique physiology of the blood–brain barrier (BBB), which is designed not only to protect the brain from exogenous and endogenous toxins but also to prevent the full cytotoxic effects of most therapeutics on intracranial tumors. Thus, many groups are developing novel methods of permeabilizing the BBB to treat infiltrating tumor cells that are in regions of normal brain. One focus of these efforts to circumvent the BBB is using novel ultrasound technology that is emerging as a noninvasive and translational approach to safely allow systemic therapies to access GBM.

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## Image-Guided, Remote-Controlled Opening of the BBB for Systemic Brain Tumor Therapy

### HIGH-INTENSITY FOCUSED ULTRASOUND IN REMOTELY OVERCOMING OF THE BBB FOR DRUG DELIVERY

High-intensity focused ultrasound (HIFU) is a therapeutic ultrasound technique that delivers high-intensity acoustic energy to a localized area in the body. These ultrasound waves are significantly higher than what is commonly used in imaging or diagnostic ultrasound. HIFU can thus be used to ablate tissue from the resulting high temperature without affecting the surrounding tissues. This is accomplished by focusing an ultrasound beam via acoustic lens, a curved transducer or a phased array (2–4). Since ultrasound waves pass through skin and other intervening tissues at relative low intensities, they produce no effect or damage outside the area of focus, where they typically provide intensities up to three to four orders of magnitude higher compared to the unfocused beam (3).

When used for therapeutic purposes, the focused ultrasound energy from HIFU induces a temperature rise or intensive mechanical force to alter tissue structure and functions, resulting in a large variety of localized bioeffects through

either mechanical or thermal activity (5). Depending on the energy level, the generated bioeffects can be mild and nondestructive, such as those for hyperthermia or physical therapy, or more extreme and destructive, such as thermal ablation of tumors in prostate, uterus, brain, etc. (6–12). Although destructive ultrasound exposures for ablation of a variety of tumors are currently the best-known application of HIFU technology, there is increasing interest in using nondestructive HIFU to induce BBB opening to allow the delivery of therapeutic agents to the brain.

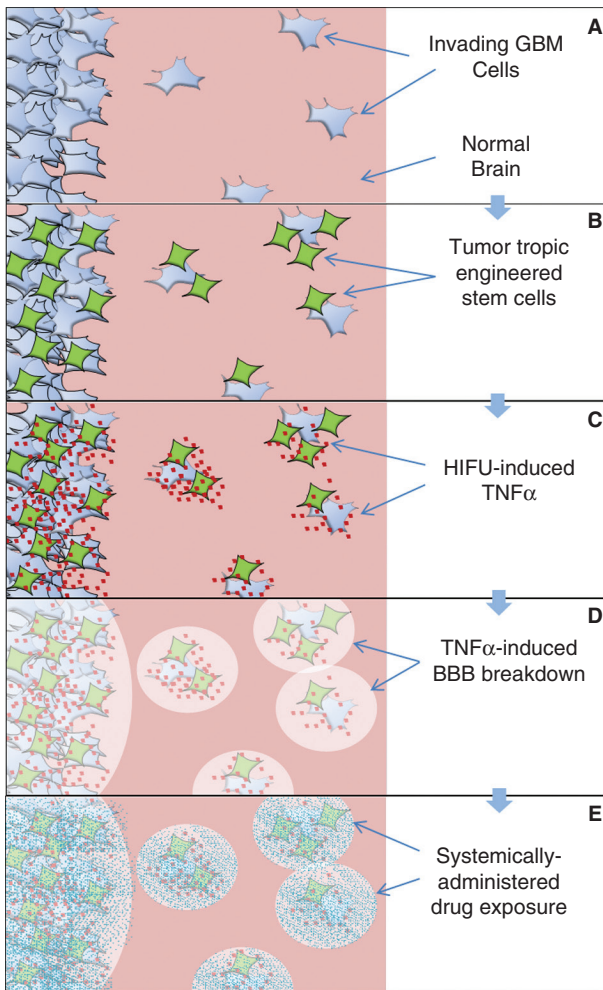
HIFU has been studied to treat brain diseases as far back as the 1940s (4, 13, 14). Localized and reversible BBB disruption created by direct sub-lethal HIFU exposure with or without pre-injection of microbubbles has been reported extensively in recent decades (5, 15, 16). Direct HIFU exposure without any ultrasound contrast agent may in itself induce BBB disruption, but tissue necrosis due to the high energy makes this technique suboptimal. By introducing microbubbles, which are typically used in diagnostic ultrasound as a contrast agent, at the time of sub-lethal HIFU exposure, researchers have demonstrated the potential of permeabilizing the BBB without producing any apparent neuronal damage (5, 17). The mechanism of this disruption is thought to be from the mechanical forces created by the oscillation of circulating microbubbles driven by focused ultrasound. This phenomenon may change the array of endothelial cells in the blood vessel wall, thus transiently increasing the permeability of the BBB without any lethal effects (18).

Although different imaging modalities have been used to guide the targeting of HIFU exposures in the body, MRI presents the standard modality in the studies for HIFU-induced BBB opening. Compared to other imaging modalities such as diagnostic ultrasound, MRI enables more accurate placement of the HIFU beam in the brain, and the delivery of gadolinium-based MR contrast agents can be used as a reliable surrogate marker for successful permeability enhancement and optimization. Thus, it is hopeful that nondestructive HIFU technologies can permeabilize the BBB to systemic therapeutics that cannot be currently used against brain cancer due to exclusion by the BBB.

## CONTROLLABLE DRUG DELIVERY USING STEM CELLS IN CONJUNCTION WITH HIFU

One of the primary reasons of GBM recurrence is the presence of infiltrating tumor cells that can be found at distances far away from the primary tumor. These cells do not permeabilize the BBB to standard gadolinium contrast and are thus not visible on MRI. Using HIFU with microbubbles to permeabilize the BBB requires visualization of the target, which may be insufficient in regions of undetectable invasive cells at a far distance from the tumor (Figure 1A). Xiong et al. have developed a HIFU technique used in conjunction with therapeutic stem cells to access these infiltrating tumor cells using the tumor-homing biological properties of stem cells to locate the invisible invasive tumor cells.

Due to their tumor-tropic capacity, stem cells are emerging as feasible delivery vehicles to therapeutically target primary and invasive tumor cells (Figure 1B). Investigators have demonstrated the *in vivo* migratory capacity of stem cells toward primary GBM tumors as well as invasive tumor cells that intermingle with normal brain tissue (19–28). Various stem cells such as embryonic stem cells,



**Figure 1** Schemata of invasive GBM cells and how they can be targeted by a combination of stem cells and HIFU. (A) Invasive GBM cells migrating away from the primary tumor mass. (B) These cells have been shown to be targeted by engineered stem cells capable of secreting therapeutics, including  $TNF\alpha$ . (C) Mild heating by HIFU can induce stem cells that express  $TNF\alpha$ , which is engineered to be under the control of the HSP70 promoter. (D)  $TNF\alpha$  causes local BBB breakdown, allowing for systemically injected therapeutics to precisely target areas of tumor invasion but not areas that are not targeted by engineered stem cells (E).

mesenchymal stem cells, neural stem cells, induced pluripotent stem cells (iPSCs), and neural stem cells derived from iPSCs have been shown to migrate to intracranially established GBMs when implanted loco-regionally within the brain, and their ability to secrete anti-GBM therapies after genetic modification has been investigated (29). The reason for the migration of stem cells toward sites of GBM and the molecular pathways involved in this process are under further investigation. Evidence suggests that the tumor tropism of stem cells is due to their affinity to the tumor microenvironment which often mimics aspects of the stem cell niches, such as by releasing various cytokines, the presence of severe hypoxia, and extensive vascularization (30, 31). Even though various chemokine receptors and their ligands have been attributed to play a role in tumor-tropic migration of stem cells, the stromal derived factor-1 (SDF-1) CXC-chemokine receptor 4 (CXCR4)

signaling axis is the most studied, and is implicated to play an important role in migration of various stem cells towards tumors (32, 33). In addition to SDF-1/CXCR4 axis, other signaling pathways such as urokinase-type plasminogen activator (uPA)/uPA receptor, PI3K, vascular endothelial growth factor receptor 2 (VEGF2), and matrix metalloproteinase 1 (MMP1)/protease-activated receptor 1 (PAR1) signaling pathways have been implicated in migration of stem cells to sites of tumors (29). SDF-1 has been reported to play a vital role in NSC maintenance and regulates NSC homing during neurogenesis (34). SDF-1 is reported to be expressed and secreted by GBM stem cells and endothelial cells which implicate its role in GBM stem cell migration and recruitment of other components of the tumor microenvironment as well. SDF-1 is also highly expressed in regions of hypoxia within GBMs and is thought to promote survival through activation of NF- $\kappa$ B (33, 35).

Various tumor-tropic stem cells have previously been reported to deliver anti-GBM therapies using different strategies. Stem cells genetically modified to express tumor necrosis factor–related apoptosis inducing ligand (TRAIL) have been used previously in preclinical studies to induce apoptosis in tumor cells. Tumor-tropic stem cells that express ligands that inhibit tumor specific receptors such as EGFRvIII and stem cells that express “decoy” receptors that sequester essential paracrine factors within the tumor microenvironment have been shown to reduce GBM cell proliferation in preclinical studies (36). Another strategy of inducing secretion of cytokines is to increase recruitment of cytotoxic T cells and anti-tumor immunity within GBM microenvironment. This strategy could also be used to in combination with immune checkpoint inhibitors to enhance tumor-directed cytotoxicity. In addition, tumor-tropic stem cells have also been shown to deliver nanoparticles loaded with chemotherapy and oncolytic viruses. The accumulation of effective concentrations of nanoparticles within GBM tissue could be increased using a stem cell–based strategy to bypass the BBB (37, 38). The efficiency and safety of delivering GBM-targeted oncolytic viruses have also been enhanced using tumor-tropic stem cells (39, 40). Thus, it has been established that using engineered stem cells to secrete therapeutics after migrating to tumor sites has strong therapeutic potential.

The biologic targeting of stem cells along with the spatial targeting of HIFU can be combined to create a remote-controlled expression platform has been leveraged to assist in locally opening up the BBB for facilitated drug delivery of systemically administered agents (41). This can be accomplished by remotely triggering expression of effector cytokines, such as TNF $\alpha$ , from engineered tumor-homing stem cells in response to noninvasive image-guided HIFU (Figure 1C). Recently, such an application of nondestructive HIFU has been used to heat tissue to nonlethal temperatures (~42°C) to locally activate the upregulation of a number of genes including heat shock protein (HSP) (42, 43). This biology has enabled investigators to *in vivo* regulate genes of their choice by engineering them to be expressed under the control of the HSP70 promoter and activating expression *in vivo* using sub-lethal HIFU (44). By combining stem cell delivery, heat-inducible gene expression and mild heating with HIFU, Xiong et al. demonstrated that HIFU can be used to remotely control the expression of pro-inflammatory factors engineered in stem cells under the control of the HSP70 promoter (Figure 1C). This targeted expression led to the permeabilization of the BBB with high-spatiotemporal precision and biologic selectivity, allowing for penetration of

systemically administered small molecular MRI contrast agent and 300-nm-sized nanoparticles into the brain (Figure 1D, E) (41). This opening of the BBB was limited to where selected factors were secreted secondary to HIFU activation, near the engineered stem cells and consequently the infiltrating tumor cells. A major advantage of this process over using focused ultrasound and microbubbles for BBB opening is the fact that this process relies on the combination of physical energy deposition and a biologic response (stem cell tumor tropism). Thus, although a much larger volume would need to be heated by HIFU to nonlethal temperatures (42–43°C), the BBB opening will be much more focused and enhanced only where the heated engineered stem cells are located, which has been demonstrated to be adjacent to primary and invasive GBM cells (Figure 1D, E) (2–4, 16–20). Although there is an added component of therapeutic stem cells, this technique can potentially be performed in a noninvasive manner, as the engineered stem cells can be placed directly into a GBM resection cavity during standard-of-care surgery using an encapsulation technique. This approach was developed by Kauer et al. who demonstrated that encapsulating therapeutic stem cells in biodegradable, synthetic extracellular matrix (sECM) significantly increased their retention time in the GBM resection cavity, permitted strong tumor-selective migration and allowed secretion of anti-tumor proteins from sECM-encapsulated stem cells *in vivo* (45). Seven to fourteen days post stem cell implantation/tumor resection, HIFU can be used to noninvasively mildly heat (42–43°C) the resection cavity and surrounding brain to activate stem cell TNF $\alpha$  production and selectively permeabilize the BBB where the stem cells migrate, including the infiltrating tumor cells. Of translational relevance, there is already a clinical HIFU system (InSightec) that is being used to transcranially treat brain disorders and is in clinical trials for brain cancer (46–48). This MRI-compatible helmet-like device houses a multi-channel-phased array system and can cover large volumes. Since one only needs to heat the brain and tumor to 42–43°C for gene activation under the HSP70 promoter, this technique is not constrained to only treating focal areas, a restriction that may limit the treating volume for reaching ablation temperatures (55°C). Heating to 42–43°C only requires a fraction of the energy needed for ablation and is feasible over large volumes in preclinical and clinical settings and does not result in overheating of the skull seen with conventional ablative HIFU. For example, an early clinical trial in using HIFU for brain tumors reported “The skull area that the acoustic beam was distributed over was calculated by the treatment planning workstation to be 284, 327, and 354 cm<sup>2</sup>, for patients 1–3” (48). Importantly, all patients received heat treatment to at least 42°C, indicating the translational potential of gently heating large areas of the brain to nonablation temperatures.

One enabling technology to controlled sub-lethal HIFU activation is MR thermometry, which incorporates automated, real-time feedback control of a pre-defined temperature, allowing for stably controlling HIFU to heat the brain tissue to around 42–43°C for successful gene activation to open the BBB (41). Indeed, transcranial magnetic resonance-guided focused ultrasound (tsMRgFUS), which employs a phase array comprised of hundreds of transducer elements, has been used in clinical trial to precisely heat or ablate target areas in the brain (49). A commercially available clinical tsMRgFUS system (inSightec Inc. Tirat Carmel, Israel) that is being used to transcranially treat various brain disorders including essential tremors, Parkinson’s disease, and brain cancer. The availability of clinical

tsMRgFUS system that can deliver HIFU energy through the human skull to a focal spot in the brain may further facilitate the translational and clinic application of using nondestructive HIFU to induce BBB opening to allow the delivery of therapeutic agents to the brain.

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## Conclusion

In order to better treat GBM, it will be crucial to develop novel techniques to deliver chemotherapies and novel molecular-targeted therapies to invasive GBM cells. HIFU provides a remote-controlled platform to permeabilize the BBB using mechanical forces via microbubbles or by mildly heating areas to induce engineered stem cells to secrete select cytokines. Translating these and other novel delivery approaches have the potential to enable significantly improved outcomes that have eluded patients receiving traditional systemic therapies.

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