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Development of skull-implanted ultrasound for blood-brain barrier opening and drug delivery in neuro-oncology

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Abstract

The blood-brain barrier (BBB) poses a significant challenge for the treatment of brain tumors as it limits the passage of most circulating drugs into the brain. Low-intensity ultrasound with microbubbles safely and transiently opens the BBB, improving drug delivery to the brain. Skull-implanted ultrasound devices are particularly effective as they allow ultrasound waves to bypass the skull. In addition, this technology has enabled sonication procedures to be performed without the need for real-time imaging guidance, neuronavigation, or MRI. Here, we review recent advancements in skull-implanted ultrasound for BBB opening and drug delivery in neuro-oncology. We highlight key preclinical and clinical studies demonstrating the safety of repeated BBB opening using skull-implanted ultrasound devices and discuss the expanding field with the activation of up to 9 implanted ultrasound emitters simultaneously. We also summarize pharmacokinetic studies supporting the efficacy of this strategy for enhanced drug delivery to the brain. In addition, we examine evidence on the temporal dynamics of BBB restoration post-sonication in brain tumor patients, emphasizing the importance of optimizing drug delivery timing. At last, we address current challenges and explore future directions for this promising therapeutic strategy.

Key Points

- Repeated blood-brain barrier opening for enhanced drug delivery is safe in humans.
- Low-intensity pulsed ultrasound and microbubbles lead to a multifold and sustained increase in parenchymal drug levels.
- Drug delivery timing should be optimized to align peak plasma concentration with BBB opening.

In the United States, malignant brain tumors account for approximately 17,000 deaths per year.[1] Among primary brain tumors in adults, glioblastoma (GBM) is the most malignant, portends a poor prognosis, and is particularly challenging to treat.[1,2] It is also the most common primary malignant brain tumor in adults and has an incidence rate of 2–3 per 100,000 individuals in the United States.[1] Despite decades worth of research and a multimodal treatment that includes surgery, chemotherapy, radiation, and tumor-treating fields, the median overall survival remains limited to around 21 months.[1,3] The ongoing challenge of managing this type of cancer continues to drive research efforts toward developing innovative and more effective treatment options.

One of the main obstacles in treating neurological diseases, and in particular infiltrative gliomas like GBM, is the blood-brain barrier (BBB), as this barrier restricts the brain penetration of most systemically administered drugs.[4] Temozolomide,

the standard of care for the treatment of primary GBM, has a brain permeability (brain-to-plasma AUC ratio) of approximately 18%.[5] It exhibits an increased efficacy over other chemotherapeutic agents that might have more potent effects on GBM in vitro but that exhibit poor penetration across the BBB.[6,7] In this context, strategies aimed at overcoming the limitations of the BBB have been employed, including local delivery of chemotherapy[8] and the use of high-osmotic solutes for transient BBB disruption.[9] Local delivery procedures such as intracranial injections offer the benefit of delivering drugs directly and accurately to the tumor or resection cavity.[10,11] Another technique, convection-enhanced delivery, utilizes pressure gradients to achieve better drug diffusion throughout the peritumoral brain parenchyma.[9,12,13] While these strategies are promising, a limitation includes the associated inconsistent distribution of drugs throughout the parenchyma.[14,15]

More recently, low-intensity pulsed ultrasound coupled with microbubble injections has emerged as a technology that can locally and non-invasively disrupt the BBB.[16–19] Preclinical studies demonstrated that ultrasound waves delivered at low intensities in conjunction with microbubbles safely and transiently open the BBB with limited damage to surrounding tissue or neurons,[17] and improve the delivery of chemotherapies[20] and immunotherapies.[21] Several iterations of this technology have been developed for clinical use, such as ExAblate (Insightec) and NaviFUS (NaviFUS corporation), which rely on the delivery of ultrasound waves through the skull using phased-array systems.[22,23] Yet, a major shortcoming of transcranial ultrasound is its attenuation by the skull.[16] This technology hence often relies on the use of phased-array systems, focused ultrasound beams, and methods to correct for skull impedance.[16,24]

In this context, skull-implantable ultrasound devices have been developed to provide an alternative for safe and repeated opening the BBB, bypassing skull hindrance (**Figure 1**).[25] This strategy has been investigated in multiple clinical trials attesting to its safety and efficacy for enhanced drug delivery.[25–27] In this review, we provide a comprehensive overview of preclinical and clinical studies evaluating the safety and efficacy of skull-implantable ultrasound devices.

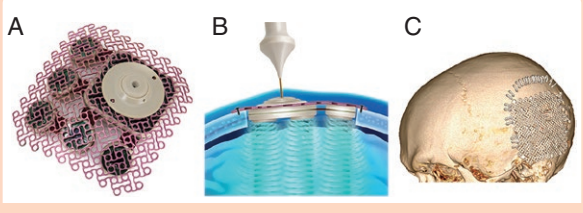

Figure 1. Design of a skull-implantable ultrasound device for blood-brain barrier opening. (A) SonoCloud-9 device consisting of a system of 9 ultrasound emitters implanted into the skull and (B, C) activated using a transdermal needle. (C) 3D reconstructed computed tomography scan illustrating the implanted SonoCloud-9 device. Adapted from Sonabend AM et al., Lancet Oncol, 2023; used with permission.

Development of Therapeutic Ultrasound for Blood-Brain Barrier Opening

Initial reports of BBB disruption with ultrasound date back to the 1960s.[28,29] At that time, therapeutic ultrasound was primarily used at high intensities for thermal ablation of tissue.[28,29] In this context, ultrasound-induced BBB disruption was recorded as a byproduct of thermal ablation at peak ultrasound intensities reaching up to 7,000 W/cm^2.[28] In the following years, the importance of BBB disruption for improved drug delivery was increasingly recognized and the sonication parameters were refined to selectively disrupt the BBB without damaging the surrounding nervous tissue.[16,17] To achieve this goal of a safe and controlled disruption of the BBB, the acoustic intensity was decreased to a range often below 10–20 W/cm^2,[30] and sonication procedures were performed in the presence of systemically injected microbubbles.[17] Low-intensity ultrasound waves induce the oscillation of microbubbles within blood vessels and the subsequent mechanical disruption of tight junctions.[31,32] In rabbits, a safe BBB disruption was noted at acoustic pressures as low as 0.4 MPa, while increasing the pressure to 2.3 MPa or higher induced tissue necrosis in most instances.[16]

Several transcranial ultrasound devices are currently under clinical investigation for BBB disruption in neuro-oncology. For instance, the ExAblate system (Insightec) consists of a hemispherical array of 1024 transducers operating at 220 kHz and coupled to a Cosman–Roberts–Well stereotactic frame for magnetic resonance imaging (MRI)-guided ultrasound delivery.[19,22,33] With this strategy, ultrasound-induced BBB disruption is performed under MRI monitoring to evaluate the cavitation dose and avoid micro-hemorrhages.[22] The first-in-human clinical trial investigating this technology demonstrated that MRI-guided focused ultrasound (MRgFUS) could be safely and repeatedly administered in the outpatient setting and improved the penetration of trastuzumab into brain metastases.[33] Its use for delivering other chemotherapies[34] and antibodies (NCT05879120) is under clinical investigation and is reviewed in **Table 1**. A similar strategy consists of using MRI-based navigation with ultrasound (NaviFUS, NaviFUS corporation), bypassing the need for MRI on the day of treatment.[23] The NaviFUS device consists of a hemispherical array of 256 phased-array transducers coupled to a neuronavigation system.[23] An ongoing clinical trial is investigating its use for the improved delivery of bevacizumab (NCT06329570).[44] A similar navigation-based transcranial ultrasound device has been developed at Columbia University, New York, using a single-element 0.25 MHz transducer,[45] and is currently under clinical investigation for the treatment of Alzheimer's disease (NCT04118764)[41] and diffuse midline glioma (NCT04804709). A list of completed and ongoing clinical trials with this strategy can be found in **Table 1**. Another neuronavigation-based ultrasound device composed of several transducers (0.65 MHz, Imasonic, France) coupled to BrainSight's neuronavigation system (Canada), is currently under clinical investigation at the Washington University in St Louis for sonobiopsy.[43,46] These strategies remain limited in terms of sonication parameters that can

Table 1. Table Illustrating Clinical Trials Registered in clinicaltrials.gov Investigating the Use of Ultrasound Technologies for Blood-Brain Barrier Disruption in Neuro-oncology

Title	Device	Phase	Location	Status	NCT ID	Ref.
Safety of BBB Opening with the SonoCloud (SONOCLOUD)	SonoCloud-1	1/2	France	Completed	NCT02253212	26,35
Ultrasound-Based Blood-Brain Barrier Opening and Albumin-Bound Paclitaxel and Carboplatin for Recurrent Glioblastoma (SC9/ABX)	SonoCloud-9	1/2	United States	Phase 1 completed, Phase 2 ongoing	NCT04528680	27
Safety and Efficacy of Transient Opening of the Blood-Brain Barrier (BBB) With the SonoCloud-9 (SC9-GBM-01)	SonoCloud-9	1/2	France United States	Completed	NCT03744026	27,36
A Randomized, Open-Label, Multicentric, Two-Arm Pivotal Trial of SonoCloud-9 Combined With Carboplatin (CBDCA) vs Standard of Care Lomustine (CCNU) or Temozolomide (TMZ) in Patients Undergoing Planned Resection for First Recurrence Glioblastoma	SonoCloud-9	3	Belgium France Germany Italy Netherlands Spain Switzerland United States	Ongoing	NCT05902169	
Innovative SonoCloud-9 Device for Blood-Brain Barrier Opening in First-Line Temozolomide Glioblastoma Patients (SonoFIRST)	SonoCloud-9	2	Belgium France Switzerland	Ongoing	NCT04614493	
Safety Study of the Repeated Opening of the Blood-Brain Barrier With the SonoCloud Device to Treat Malignant Brain Tumors in Pediatric Patients (SONOKID)	SonoCloud-9	1	France	Ongoing	NCT05293197	
Phase 2a Immune Modulation With Ultrasound for Newly Diagnosed Glioblastoma	SonoCloud-9	2	United States	Ongoing	NCT05864534	
Efficacy and Safety of NaviFUS System Add-on Bevacizumab (BEV) in Recurrent GBM Patients	NaviFUS	N/A	Taiwan	Completed	NCT04446416	
Safety of BBB Disruption Using NaviFUS System in Recurrent Glioblastoma Multiforme (GBM) Patients	NaviFUS	N/A	Taiwan	Completed	NCT03626896	
Evaluate the Safety and Preliminary Efficacy of the Combination of NaviFUS System With Re-irradiation for rGBM Patients	NaviFUS	N/A	Taiwan	Ongoing	NCT04988750	
Safety and Efficacy of Bevacizumab in Combination With NaviFUS System for the Treatment of Recurrent Glioblastoma Multiforme (rGBM)	NaviFUS	1/2	United States	Not yet recruiting	NCT06329570	
Blood-Brain Barrier Disruption (BBBD) Using MRgFUS in the Treatment of Her2-Positive Breast Cancer Brain Metastases (BBBD)	ExAblate	N/A	Canada	Completed	NCT03714243	33
Blood-Brain Barrier Disruption Using Transcranial MRI-Guided Focused Ultrasound	ExAblate	1	Canada	Completed	NCT02343991	37
Assessment of Safety and Feasibility of ExAblate Blood-Brain Barrier (BBB) Disruption	ExAblate	N/A	United States	Completed	NCT03551249	
ExAblate Blood-Brain Barrier Disruption (BBBD) for Planned Surgery in Suspected Infiltrating Glioma	ExAblate	0	United States	Completed	NCT03322813	38
Assessment of Safety and Feasibility of ExAblate Blood-Brain Barrier (BBB) Disruption for Treatment of Glioma	ExAblate	N/A	Canada	Completed	NCT03616860	39
ExAblate Blood-Brain Barrier Disruption for Glioblastoma in Patients Undergoing Standard Chemotherapy	ExAblate	N/A	Republic of Korea	Completed	NCT03712293	34,40
ExAblate Blood-Brain Barrier Disruption for the Treatment of rGBM in Subjects Undergoing Carboplatin Monotherapy	ExAblate	1/2	United States	Ongoing	NCT04417088	
ExAblate Blood-Brain Barrier Disruption With Carboplatin for the Treatment of rGBM	ExAblate	1/2	Canada Italy Republic of Korea	Ongoing	NCT04440358	

Table 1. Continued

Title	Device	Phase	Location	Status	NCT ID	Ref.
Blood-Brain Barrier (BBB) Disruption Using ExAblate Focused Ultrasound with Standard of Care Treatment of NSCLC Brain Mets	ExAblate	3	Canada Republic of Korea United States	Ongoing	NCT05317858	
Blood-Brain Barrier (BBB) Disruption Using ExAblate Focused Ultrasound with Doxorubicin for Treatment of Pediatric DIPG	ExAblate	1/2	Canada United States	Ongoing	NCT05615623, NCT05630209	
Extracellular Impact of Ultrasound-Induced Blood-Brain Barrier Disruption	ExAblate	N/A	United States	Ongoing	NCT05733312	
Randomized Study of Neo-adjuvant and Adjuvant Pembrolizumab With and Without Targeted Blood-Brain Barrier Opening Using ExAblate MRI-Guided Focused Ultrasound (ExAblate MRgFUS) for Recurrent Glioblastoma	ExAblate	2	United States	Ongoing	NCT05879120	
Safety and Effectiveness of Blood-Brain Barrier Disruption (BBBD) in Subjects With Suspected Infiltrating Glioma (BBBD)	ExAblate	N/A	United States	Ongoing	NCT04667715	
Assessment of Safety and Feasibility of ExAblate Blood-Brain Barrier (BBB) Disruption in GBM Patients	ExAblate	N/A	Italy Spain	Unknown	NCT04998864	
Blood-Brain Barrier Disruption (BBBD) for Liquid Biopsy in Subjects With GlioBlastoma Brain Tumors	ExAblate	1	Canada United States	Ongoing	NCT05383872	
Non-invasive Blood-Brain Barrier Opening in Alzheimer's Disease Patients Using Focused Ultrasound.	N/A	N/A	United States	Ongoing	NCT04118764	41,42
Non-Invasive Focused Ultrasound (FUS) With Oral Panobinostat in Children With Progressive Diffuse Midline Glioma (DMG)	N/A	1	United States	Ongoing	NCT04804709	
Sonobiopsy for Non-invasive and Sensitive Detection of Glioblastoma	N/A	N/A	United States	Ongoing	NCT05281731	43

be used due to skull absorption and distortion of ultrasound, which is challenging to characterize and may lead to the dissipation of acoustic energy as heat, or acoustic parameters that lead to excessive cavitation activity/mechanical effects that could lead to hemorrhage.[47] This limitation is offset by the use of phased-array transducers, technologies that correct for distortion by the skull, and real-time acoustic monitoring to control bubble/cavitation activity.[16,24,48]

Over the last decade, skull-implantable, MRI-compatible, ultrasound transducers have been developed by Carthera.[48] The initial design consisted of a single ultrasound transducer (SonoCloud-1, 10 mm in diameter) delivering unfocused low-intensity pulsed ultrasound (LIPU).[25] These ultrasound beams delivered as pulses minimize potential thermal damage to surrounding tissue while enabling the delivery of a controlled acoustic energy.[29] The latest version of skull-implantable ultrasound devices, SonoCloud-9, features 9 ultrasound transducers (10 mm in diameter each) (**Figure 1**)[27,36] covering a larger sonication field than the first-generation SonoCloud-1 device (which consisted of a single ultrasound emitter).[25] Strategic placement of the device within a skull window overlying the region of interest is crucial as it enables sonication procedures to be subsequently performed in an outpatient setting without the need for MRI guidance or neuronavigation. This strategy has been investigated in multiple clinical trials, primarily performing sonication procedures over the peritumoral brain after the device was implanted into the skull during surgeries for resection of the recurrent tumor.[25–27] Ongoing clinical trials also investigate its use in the context of primary glioma, as illustrated in **Table 1**. We review below the preclinical and clinical evidence attesting to the safety and efficacy of skull-implantable ultrasound technology for BBB opening and drug delivery.

Safety of Skull-Implanted Ultrasound for Blood-Brain Barrier Opening

Skull-implanted ultrasound for BBB opening was first investigated in rabbits in 2013, where experiments were performed to verify safe acoustic parameters for BBB disruption.[48] Single-sonication procedures at acoustic pressures ranging between 0.3 and 0.8 MPa, pulse repetition frequency of 1 Hz, and pulse lengths of 10–35 ms resulted in localized BBB opening with limited side effects except at the highest parameters (0.8 MPa, pulse length of 35 ms), which resulted in hemorrhagic lesions.[48] BBB disruption was found to correlate with pulse length and acoustic pressure, and the efficacy of BBB disruption decreased in deep brain structures away from the ultrasound device.[48] Subsequent preclinical studies demonstrated improved delivery of chemotherapies such as Temozolomide and Irinotecan.[49] Next, a biocompatible version of the device

that could be implanted in a 12-mm skull burr hole was developed and tested in non-human primates demonstrating the safety of repeated BBB disruption over eloquent brain regions, and demonstrated a 5.2-fold increase in carboplatin levels following systemic administration.[50,51] The study demonstrated the absence of ultrasound-induced epileptic discharges.[50] It is, however, important to note that primates were anesthetized during the sonication procedure, which could have prevented epileptic discharge formation.

A first-in-human phase 1/2 clinical trial (NCT02253212) investigating skull-implanted ultrasound in humans was performed using a single-emitter 1 MHz ultrasound device (SonoCloud-1) to deliver carboplatin in patients with recurrent GBM.[26] This trial enrolled 21 patients, of whom 19 received LIPU with microbubbles (LIPU/MB). To determine the safe acoustic parameters, the dose-escalation trial investigated acoustic pressures ranging from 0.41 to 1.15 MPa, and treatment was administered every 4 weeks until disease progression or evidence of dose-limiting toxicity or serious adverse events. A total of 65 sonication cycles were performed with patients tolerating up to 10 sonication cycles at doses reaching up to 1.15 MPa.[26] Two instances of sonication-related, steroid-responsive, edema were reported and there were limited side effects related to sonication. BBB opening was successful in 52 instances (80%) and correlated with delayed tumor progression.[26] Importantly, this trial established the safe acoustic parameters for skull-implanted ultrasound-based BBB disruption in humans.

The safety of LIPU/MB using a single-emitter skull-implanted ultrasound device paved the way for clinical trials investigating the use of a larger 9-emitter device (SonoCloud-9) enabling a broader disruption of the BBB. An initial phase 1 clinical trial (NCT03744026) evaluated the safety of activating an increasing number of emitters and demonstrated that all 9 ultrasound emitters could be safely and concomitantly activated.[36] In a parallel phase 1 clinical trial (NCT04528680), the safety of delivery of paclitaxel was investigated while activating all nine emitters.[27] LIPU/MB using this 9-ultrasound emitter device led to a median depth of disruption of 64 mm (**Figure 2**).[36]

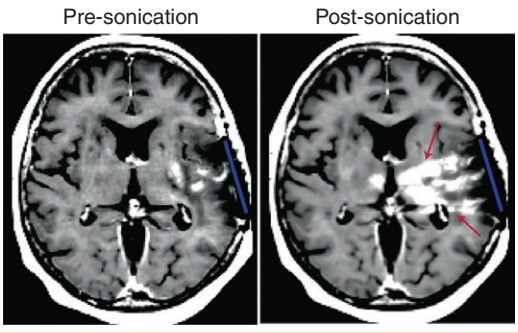

Figure 2. Contrast-enhanced MRI illustrates the disruption of the blood-brain barrier following low-intensity pulsed ultrasound with microbubbles. The line shows the position of the implanted SonoCloud-9 device and the arrows illustrate the area of blood-brain barrier disruption. Adapted from Carpentier A et al., Nature Commun, 2024.

Overall, these three clinical trials enrolled a total of 70 patients who received skull-implanted LIPU/MB for improved drug delivery in the context of GBM treatment. The most commonly reported side effects were unrelated to LIPU/MB but rather to the administrated chemotherapy. We review the most common ultrasound-related adverse events in **Table 2**. Importantly, surgical site infections (SSIs) were rare overall (incidence < 5%), with a rate comparable to craniotomy-associated SSI,[52] and no device removal was needed in any of the trials. Similarly, seizure rates were low, and only 3 patients experienced a seizure classified as grade 3 or 4. Headaches emerged as the most common adverse event, with a total incidence of 31% across all studies and were primarily of mild intensity. Notably, headache and seizure rates were variable across studies, with higher rates recorded in the NCT04528680 (Sonabend et al.) clinical trial.[27] This variability could be multifactorial, and there are various potential differences between the studies that could contribute to this. For instance, the more deliberate use of steroids and anti-epileptic drugs in the other trials, as well as the single ultrasound emitter implant investigated in NCT02253212 (Idbaih et al.) clinical trial,[26] compared to 9 emitters in the other 2 trials[27,36] could have influenced adverse event rates. The second most common adverse event reported was pain at the needle insertion site used to connect the implanted ultrasound device to the power source (19%), followed dizziness of mild intensity (17%). Instances of transient focal neurological deficits, such as extremity weakness, aphasia, or dysarthria, were reported. The symptoms were somatotopically congruent, and all patients recovered their function within hours of sonication. Two patients (3%) among the entire cohort of 70 patients experienced a stroke.

Improved Drug Delivery to the Human Brain with Skull-Implanted Ultrasound

While early preclinical studies in rodents and non-human primates demonstrated that LIPU/MB improves the delivery of chemotherapies to the brain,[49,51] evidence in humans became apparent through pharmacokinetic studies conducted in 2 clinical trials, NCT04528680 and NCT03744026.[27] In these trials, the 9-ultrasound emitter device (SonoCloud-9) was implanted into a skull window during surgery for resection of recurrent GBM and patients received LIPU/MB for improved delivery of nab-paclitaxel (Abraxane) or carboplatin. In instances where sonication procedures and infusion of chemotherapy were administered intraoperatively, biopsies from sonicated and non-sonicated brain regions were taken for drug quantification.[27] It is important to note that these pharmacokinetic studies focused on drug levels within the peritumoral brain surrounding the resection cavity, as it is the site of up to 90% of recurrences and typically maintains an intact BBB.[53,54] Notably, these studies illustrated that LIPU/MB increases brain parenchymal concentrations of nab-paclitaxel and carboplatin by 3.7- and 5.9-fold,

Table 2. Table Illustrating Ultrasound-Related Adverse Events Observed Across the Three Completed Clinical Trials Investigating Skull-Implantable Ultrasound Devices for Neuro-oncology

Adverse event	Idbaih A, 2019	Sonabend AM, 2023	Carpentier A, 2024	Total
	(*n* = 19)	(*n* = 17)	(*n* = 34)	(*n* = 70)
Headache				
All	5 (26%)	15 (88%)	7 (21%)	22 (31%)
Grades 3-4	1 (5%)	0	0	1 (1%)
Needle insertion pain during implant activation				
All	1 (5%)	6 (35%)	6 (18%)	13 (19%)
Grades 3-4	N/A	N/A	NA	NA
Dizziness				
All	1 (5%)	3 (18%)	8 (24%)	12 (17%)
Grades 3-4	0	0	0	0
Seizure				
All	0	8 (47%)	2 (6%)	10 (14%)
Grades 3-4	0	3 (18%)	0	3 (4%)
Transient facial or limb weakness				
All	4 (21%)	4 (24%)	1 (3%)	9 (13%)
Grades 3-4	0	0	0	0
Surgical site infection*				
All	0	1 (6%)	2 (6%)	3 (4%)
Grades 3-4	0	0	2 (6%)	2 (3%)

*Surgical site infection rates were comparable to those observed in regular surgeries for glioblastoma without ultrasound device implantation as reported in Nair S et al.[51]

respectively.[27] It is possible that the effect of LIPU/MB was more pronounced with carboplatin due to its lower molecular weight, yet other chemical properties of the drugs could play a role in the brain penetration following LIPU/MB.[55] An ongoing phase 2 clinical trial (NCT04528680) that we are conducting is now evaluating the safety and efficacy of using LIPU/MB to deliver both carboplatin and nab-paclitaxel as a combination.

More recently, in a similar report, we investigated the efficacy of LIPU/MB for the enhanced delivery of immunotherapeutic agents.[56] In the NCT04528680 clinical trial, 4 patients who experienced tumor progression while on nab-paclitaxel with LIPU/MB were subsequently transitioned to receive Doxorubicin (DOX) and pembrolizumab with LIPU/MB under single-patient expanded access protocols, repurposing the already implanted ultrasound devices for the new treatment regimen. Two of the patients received surgery for resection of the tumor after 2 days of therapy administration, and biopsies from sonicated and non-sonicated peritumoral brain illustrated that LIPU/MB led to a 2-fold increase in the concentrations of DOX and pembrolizumab.[56] Interestingly, this therapy led to the upregulation of HLA-ABC and HLA-DR by tumor cells and an increase in the production of IFN-γ by microglia and tumor-infiltrating $CD8^+$ and $CD4^+$T cells.[56] In summary, this evidence highlights the ability of LIPU/MB to increase the concentration of large molecules such as antibodies and liposomal drugs capable of modulating the tumor immune microenvironment of GBM. We have further explored the application of LIPU/MB for enhancing the delivery and efficacy of a novel second-generation anti-CTLA-4 antibody that exhibits enhanced binding to FcgRIIIA in host immune cells. We observed that this antibody, when combined with anti-PD-1 immune checkpoint blockade, low-dose DOX, and LIPU/MB, is highly effective in murine glioma models.[57] An ongoing phase 2a clinical trial (NCT05864534) is currently investigating the safety and feasibility of delivering DOX, PD-1, and these novel CTLA-4 blocking antibodies with LIPU/MB for the treatment of newly diagnosed GBM.

To investigate the optimal timing of drug infusion in relation to ultrasound-induced BBB opening, the dynamics of BBB repair following LIPU/MB were examined in 2 separate clinical trials.[27,36] In both trials, the extent of gadolinium enhancement on MRI obtained after LIPU/MB was quantified and used as a surrogate of BBB opening. An analysis correlating the extent of gadolinium enhancement to the time from sonication to contrast administration revealed that BBB repair starts soon after sonication and that the BBB is mostly restored within the first hour after LIPU/MB (**Figure 3**).[27,36]These studies uncovered faster BBB repair dynamics compared to earlier clinical studies that reported BBB restoration 24 hours post-sonication.[19,37,58] We performed a single cell transcriptomic and ultrastructural analysis of capillaries of sonicated human brain collected in our trial during this first hour, this critical period for BBB restoration and homeostasis. This analysis revealed that LIPU/MB led to distinct endothelial cell gene expression changes, particularly in genes related to neurovascular barrier function and structure, including genes involved in the basement membrane, endothelial cell cytoskeleton, and junction complexes, as well as caveolar transcytosis and various solute

transporters in these cells. Ultrastructural analysis showed that LIPU/MB led to a decrease in luminal caveolae, the emergence of cytoplasmic vacuoles, and the disruption of the basement membrane and tight junctions.[59] The quick repair of the BBB also emphasized the importance of optimizing the timing of drug infusion when administered with LIPU/MB.[59] In this context, the impact of treatment administration timing relative to sonication was investigated using carboplatin, with the drug administered either immediately before sonication or delayed, averaging 64 min post-sonication.[36] This analysis revealed that a better tumor control within the sonicated field was achieved when chemotherapy was administered within 15 minutes of sonication.[36] Conversely, tumor control was less remarkable when carboplatin administration was delayed, potentially due to decreased drug penetration at a time when the BBB is predominantly restored.[27] Pharmacokinetic analyses also support the rapid repair of the BBB, which can be leveraged to trap drugs in the brain. Through perioperative pharmacokinetic analyses involving intraoperative LIPU/MB and implant of microdialysis catheters, we observed that the transient BBB opening by LIPU/MB led to sustained elevations in parenchymal carboplatin concentrations, resulting in a significantly higher area under the curve for concentration over time, compared to non-sonicated brain. Notably, carboplatin reached higher parenchymal than plasma concentrations a few hours after sonication, underscoring a likely trapping of this drug in the brain interstitial space at time points where the BBB is restored.[55] The SONOBIRD trial, an ongoing randomized phase 3 clinical trial (NCT05902169) is currently investigating the efficacy of carboplatin and LIPU/MB compared to Temozolomide or Lomustine in patients with recurrent GBM.

Challenges, Limitations, and Future Directions

One of the primary limitations of skull-implantable ultrasound devices is that the sonicated region is limited by the device's coverage area and the sonication field cannot be modified once the device is implanted. There are therefore 3 inherent shortcomings: (1) Large tumors are typically excluded from ongoing trials using this technology, as the peritumoral brain where infiltrating glioblastoma cells reside, is likely to be larger than the area covered by the implanted device, limiting drug exposure to these regions; (2) Multifocal disease often cannot be encompassed by a single ultrasound device; (3) Subsequent recurrences at distant sites might not be covered by the device, or will require surgery for adjustment of the device's placement. However, while sonicating the whole tumor is crucial for maximizing cytotoxicity, abscopal effects may arise from sonicating part of the tumor. Indeed, ultrasound induces inflammation,[60] and when combined with immunomodulators such as DOX, it enhances antigen presentation by tumor cells and activates microglia.[56] It is therefore possible that even partial coverage by LIPU/MB-based BBB disruption of large tumors could trigger an anti-tumor immune response, extending the therapeutic effect beyond the sonication field. We are currently investigating the immune-modulatory aspects of this technology in an immunotherapy trial where second-generation anti-CTLA-4 and anti-PD-1 immune checkpoint blockade antibodies plus DOX are delivered with LIPU/MB to patients with MGMT un-methylated glioblastomas (NCT05864534) in the adjuvant setting. This treatment paradigm is based on our preclinical and early clinical evidence suggesting this to be a robust immunotherapy.[56,57]

Another limitation of skull-implanted ultrasound technology is that it requires surgery for placement of the device, unlike other less invasive methods of transcranial ultrasound. It also requires activation during therapy cycles, likely adding cost and potentially impacting patient compliance. While direct costs are difficult to estimate as the device is not yet commercially available, implanting it during surgery for tumor resection or through an ambulatory procedure may help offset some of these expenses. We are doing this ambulatory implant surgery as part of our ongoing immunotherapy trial (NCT05864534), supporting that implant is not a major limitation to this approach. In addition, sonication

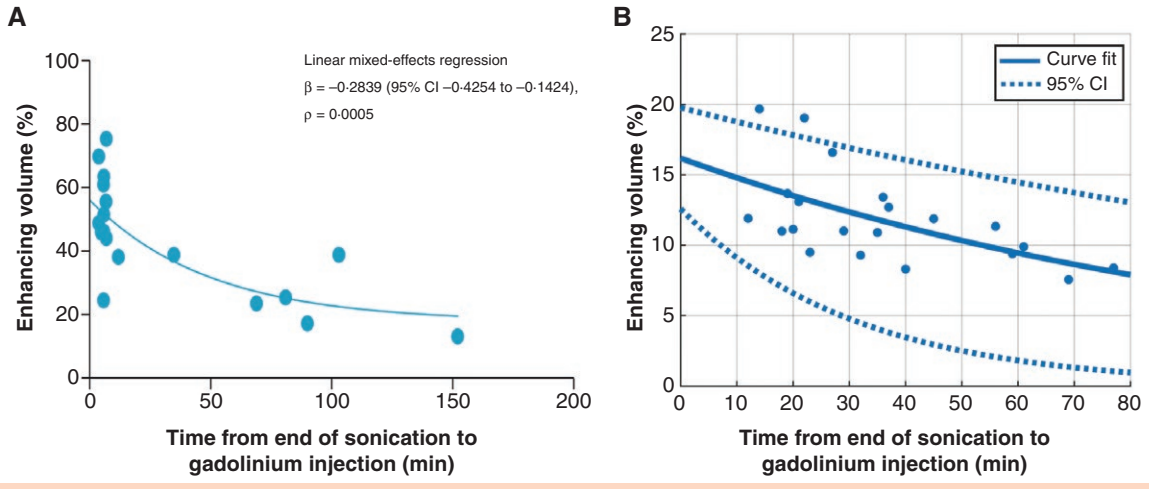

Figure 3. The blood-brain barrier is restored quickly following ultrasound. Scatter plots illustrating the volume of ultrasound-related peritumoral enhancement in relation to the time from sonication to gadolinium injection reported in (A) Sonabend AM et al., Lancet Oncol, 2023 and (B) Carpentier A et al., Nature Commun, 2024.

during therapy cycles requires 4 min per session[27] (connection of device, preparation of microbubbles, and sonication takes on average of 9 min[26]), and is performed in an outpatient setting without the need for specialized personnel or equipment, further supporting its feasibility and scalability, and its limited influence on patient compliance.

It is also crucial to understand the dynamics of BBB opening and repair and its relation to the pharmacokinetics of delivered drugs. Essentially, for optimal drug delivery to the brain, BBB opening should coincide with the peak plasma concentration of the drug. The timing of drug administration and sonication may therefore need to be optimized for specific agents and formulations. This might pose an additional challenge for oral agents that often reach peak plasma levels slower than those administered intravenously. To mitigate this challenge, oral drugs with delayed plasma peak concentrations could potentially be delivered hours before the sonication procedure, as has been done in the SonoFirst trial (NCT04614493) with Temozolomide, which peaks at around 2 to 3 hours after ingestion.[36] Drug characteristics such as molecular weight, lipid solubility, the proportion of circulating free-drug and whether the drug is cleared by efflux proteins are also likely to influence brain drug penetration and permanence following sonication. This, in part, explains the differences we observed between carboplatin and nab-paclitaxel, the latter having a higher molecular weight.[27]

Safety considerations have also been important. Early trials have focused extensively on characterizing the adverse effects of the procedure.[25–27,36] However, as applications widen and treatment regimens become more complex, especially with the use of therapies that did not reach high brain concentrations previously, long-term safety and the potential for cumulative effects warrant continued scrutiny.

So far trials evaluating this technology have shown abundant data supporting the safety, feasibility, robust drug brain penetration for various agents, the possibility of repeated treatments, and some preliminary signs of efficacy.[27,36,61] Yet, whereas drug penetration is essential, it is not sufficient to elicit durable and favorable outcomes. Ultimately, tumor biology dictates the response to treatment, and efficacy relates to the choice of drug used and the individual tumor susceptibility to a given agent. LIPU/MB is a versatile technology that does not restrict the use of a single agent, but that can rather be coupled with most drugs. This strategy opens opportunities to explore therapies that demonstrated robust cytotoxicity against gliomas in vitro, yet have been limited by poor penetration of the BBB and reduced efficacy in vivo. For instance, we and others previously reported paclitaxel as a potent chemotherapeutic against glioma cells in vitro,[7,61,62] which prompted our dose-escalation phase 1 trial evaluating the use of albumin-bound paclitaxel with ultrasound-based BBB opening,[27] as well as its combination with and carboplatin and LIPU/MB in an ongoing phase 2 trial (NCT04528680). Treating GBM is further complicated by inter-tumor heterogeneity, resulting in variable responses across patients. We therefore believe that a one-size-fits-all approach might not suffice. Efficacy might depend on combining therapies and carefully selecting patients with potential susceptibility to the investigated therapy. In addition, clinical trials investigating ultrasound-mediated drug delivery could be designed to incorporate intraoperative sonication during tumor resection or ultrasound device implantation, as we have done. This approach provides the opportunity to obtain biopsies or implant microdialysis catheters for drug quantification and assessment of drug penetration into the brain parenchyma. The parenchymal drug concentrations achieved can then be evaluated for cytotoxicity against glioma models in vitro to determine whether the desired cytotoxic effect is attainable with the concentrations in the human brain. Ultimately, anatomical and tumor-biology features (i.e., predictive biomarkers) should dictate patient selection to maximize efficacy.

Skull-implanted ultrasound is likely to have applications extending beyond the treatment of brain tumors and drug delivery. For example, it has been investigated for the treatment of Alzheimer's disease and its potential role in promoting the clearance of β-amyloid.[63] Also, similarly to studies performed with transcranial ultrasound,[64–66] skull-implanted ultrasound may have future applications for performing sonodynamic therapy and neuromodulation.

Conclusion

The use of ultrasound-based technologies in neuro-oncology has evolved significantly. Three commercial devices and 2 academic systems are currently under clinical investigation for treatments in neuro-oncology, with one skull-implantable device developed to bypass the skull and facilitate repeated treatments. Repeated ultrasound-based BBB opening has been demonstrated to be safe, and the procedure successfully increases parenchymal drug levels. While it has mainly been investigated with existing chemotherapies, the integration of this technology with emerging treatments, such as immunotherapy, gene therapy, and viral therapy, offers another promising direction. The rapid restoration of the BBB after sonication, combined with drugs that are BBB impermeable, might allow for prolonged permanence of drugs (drug trapping), and therefore increased efficacy. The ability to safely and effectively deliver these agents and their combinations to the brain could advance the treatment of numerous central nervous system conditions that are currently difficult to manage. Expanding the range of treatable central nervous conditions represents an appealing application of ultrasound-based drug delivery that warrants further exploration.

Keywords

blood-brain barrier | drug delivery | glioma | neuro-oncology | ultrasound.

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