Pharmazie

Pharmazie **2026**; 81(11): 54296
https://doi.org/10.31083/Pharmazie54296

Review

Focused Ultrasound in Combination With Microbubbles and Nanoparticles for Reversible Blood–Brain Barrier Disruption and Targeted Brain Drug Delivery: Recent Advances and Therapeutic Perspectives

Pravin Kumar Sharma[1], Mohit Patil[1], Sumeet Dwivedi[1,*], Gajanan N. Darwhekar[1]

[1]Acropolis Institute of Pharmaceutical Education and Research, 453771 Indore, Madhya Pradesh, India
*Correspondence: sumeet_dwivedi2002@yahoo.com (Sumeet Dwivedi)
Academic Editor: Hirofumi Takeuchi
Submitted: 27 May 2026 Revised: 28 July 2026 Accepted: 12 August 2026 Published: 13 November 2026

Abstract

The blood–brain barrier (BBB) remains a major obstacle in the effective treatment of neurological disorders due to its highly selective permeability, which restricts the entry of therapeutic agents into the brain. Therefore, the development of advanced and targeted drug delivery strategies is of significant importance. This review highlights an emerging triad-based approach involving magnetic resonance-guided focused ultrasound (MRgFUS), circulating microbubbles, and engineered nanoparticles for reversible and localized BBB modulation and enhanced brain drug delivery. In this strategy, FUS in combination with intravenously administered microbubbles induces temporary and controlled BBB disruption, thereby creating a safe therapeutic window for drug transport into the central nervous system. However, successful BBB opening alone does not ensure efficient drug distribution because the dense extracellular matrix of brain tissue further limits molecular diffusion. To overcome this challenge, polymeric and lipid-based nanoparticles have been explored as smart nanocarriers capable of penetrating the brain microenvironment and improving localized drug accumulation. Furthermore, surface-functionalized nanoparticles enable targeted cellular uptake and controlled or sustained drug release, thereby enhancing therapeutic efficacy for applications such as chemotherapy, gene therapy, and neuroprotective treatments. The synergistic integration of FUS, microbubbles, and nanoparticles offers a noninvasive, site-specific, and efficient platform for overcoming critical barriers associated with brain drug delivery. Overall, this triad-based system represents a promising and transformative strategy for the treatment of brain tumors, neurodegenerative disorders, and other central nervous system diseases with improved safety, precision, and therapeutic outcomes.

Keywords: focused ultrasound; blood–brain barrier; microbubbles; nanoparticles; targeted brain drug delivery

1. Introduction

Recently, the development of novel drug delivery systems (NDDSs) has revolutionized the field of drug delivery by allowing for more targeted drug delivery, longer systemic circulation, target specificity, and lower off-target toxicity. By engineering nanocarriers according to their physicochemical properties, biological interactions, and microenvironment characteristics, the therapeutic potential of nanomedicine has been further advanced in recent years. In addition, current literature has highlighted that effective clinical translation of advanced NDDS requires a realistic design strategy for each disease, scaling of manufacturing, reproducible formulation, and adherence to the latest regulatory standards, which would help close the gap between laboratory development and clinical application. Within this rapidly growing field, focused ultrasound (FUS), microbubbles, and engineered nanoparticles are the next generation of central nervous system (CNS) drug delivery strategies for targeted delivery of small molecules, biologics, nucleic acids, and gene-editing therapeutics. However, the blood–brain barrier (BBB) is still one of the major barriers in the development of those drugs for clinical use. The transient and localized BBB opening induced by FUS facilitates the site-specific delivery of many different kinds of nanocarriers to the brain, and toxicity is reduced. As such, the unification of image-guided BBB modulation with advanced NDDS is a promising strategy for precision neurotherapeutics and accelerates the clinical translation of nanomedicine for neurological disorders. Although many recent reviews have discussed focused ultrasound (FUS)-mediated blood–brain barrier opening, microbubble cavitation, or nanoparticle-based brain drug delivery, and a few have addressed FUS-microbubble systems for BBB modulation, there is an absence of a comprehensive review of the synergy of focused ultrasound, microbubbles, and engineered nanoparticles as a therapeutic framework for CNS drug delivery. The novelty of this review is that it brings these three complementary technologies in sync under the same mechanistic and translational framework; the three technologies can be used to improve and accelerate BBB opening, microbubbles can be manipulated to enhance vascular permeability, and nanoparticles can be used to deliver therapeutic agents even after BBB modulation. In addition to summarizing the technological advancements, this

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

review also discusses their interdependencies, optimization techniques, clinical translation, safety, and future applications in precision neurotherapeutics. By focusing on the integration of these three technologies rather than using discrete technologies to achieve the desired outcomes, a more holistic view of CNS drug delivery can be gained, and beyond that, where the integrated technology will be implemented into clinical practice [1].

2. The Blood–Brain Barrier (BBB) Challenge

The BBB is a highly specialized and dynamic interface that maintains the CNS homeostasis through direct communication of molecules between the bloodstream and the brain. It is composed of brain microvascular endothelial cells (BMECs) that reside in tight junctions of claudin, occludin and zonula occludens (ZO) proteins, which restrict paracellular transport. Moreover, the endothelial cells are surrounded by pericytes that are integrated into the basement membrane and astrocytic end-feet, forming the neurovascular unit (NVU). Moreover, neurons, microglia, and extracellular matrix proteins are essential for the development, maintenance, and function of the BBB in complex signalling pathways [2,3]. This multicellular environment, of which the BBB is made, is highly regulated and is necessary for the brain to function properly, to move neurons and communicate efficiently, and to protect the brain from harmful substances and pathogens. Physiologically, the BBB is limited by physical, transport, metabolic, and immunological barriers. Tight junctions limit the diffusion of hydrophilic compounds, whereas special influx transporters such as glucose transporter-1 (GLUT1) and large neutral amino acid transporter-1 (LAT1) slow the entry of essential nutrients into the brain [3,4]. ATP-binding cassette (ABC) efflux transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs) also actively expel xenobiotics and many drugs back into the systemic circulation. Furthermore, endothelial metabolic enzymes and the low rate of vesicular transcytosis provide additional protection from entering the brain and potentially harmful compounds. In spite of its critical physiological role, the BBB is still one of the most significant barriers to effective CNS drug delivery. Small-molecule drugs and nearly all biologics, such as peptides, proteins, monoclonal antibodies, gene therapeutics, and nucleic acid drugs, are not well-solvable in the brain due to poor permeability, active efflux, and enzymatic degradation. Therefore, the treatment of neurological diseases like Alzheimer's disease, Parkinson's disease, glioblastoma, epilepsy, and multiple sclerosis often becomes a challenge due to the lack of drug delivery to the target. To address these challenges, a large number of researchers have considered brain-targeting strategies such as receptor-mediated and transporter-mediated transcytosis, nanoparticle-based drug delivery systems, focused ultrasound-mediated BBB modulation, intranasal administration, cell-penetrating peptides, and biomimetic nanocarriers [4]. A comprehensive understanding of BBB structure, physiology, and transport mechanisms is crucial for the design of safe and effective CNS-targeted therapeutics.

The BBB serves as a significant physiological obstacle in creating effective neurotherapeutics, effectively rendering the CNS a "pharmacological sanctuary" [3]. Instead of functioning as a fixed physical barrier, the BBB is a dynamic and intricate structure known as the neurovascular unit (NVU) [4]. This functional unit consists of specialized capillary endothelial cells that work in close collaboration with pericytes, the end-feet of astrocytes, microglia, and neurons to carefully regulate the microenvironment of the CNS and maintain ionic balance [5,6].

The impressive impermeability of this barrier is sustained by a three-tiered defense mechanism. From a structural perspective, the endothelial cells are interconnected through continuous tight junctions (TJs), which are complex protein formations including claudin-5, occludin, and junctional adhesion molecules (JAMs), all linked to the cytoskeleton via zonula occludens (ZO-1, ZO-2) proteins [7,8,9]. These junctions eliminate aqueous paracellular pathways, limiting passive diffusion to small, lipid-soluble molecules (under 400 Da) [2]. This physical barrier is enhanced by a robust "chemical barrier" created by ABC efflux transporters, particularly P-gp and BCRP [10,11]. These transporters actively identify and expel various xenobiotics—including chemotherapy agents and antiretrovirals—back into the bloodstream, often preventing these compounds from reaching effective therapeutic levels, even after crossing the cell membrane [12].

For nanoparticulate drug delivery systems, the BBB presents an even more significant challenge. Despite the ability of nanoparticles (NPs) to encapsulate and safeguard sensitive cargos (such as genes or proteins), their size (20–200 nm) typically hinders them from accessing the healthy brain, as they exceed the dimensions of the paracellular openings [13]. Additionally, in the absence of specific surface modifications, NPs are susceptible to rapid opsonization and clearance by the reticuloendothelial system or fail to activate the highly specific receptor-mediated transcytosis pathways (such as those involving Transferrin or Insulin receptors) necessary for crossing the endothelium [14,15]. This systematic exclusion of over 98% of small-molecule drugs and nearly all large-molecule biologics is a primary factor contributing to the high failure rate of CNS drugs in clinical trials [16], highlighting the urgent need for developing active, physical disruption strategies like focused ultrasound to temporarily breach these barriers.

3. FUS-Mediated Delivery

When compared to surgical techniques that involve invasive procedures—such as convection-enhanced delivery or intracerebral injections—which pose considerable risks of bleeding, infection, and damage to adjacent tissues

[17,18], FUS stands out as a groundbreaking, non-invasive method to penetrate the BBB. The remarkable aspect of this technology is its capacity to precisely direct acoustic energy down to the millimeter level through the intact skull, often using magnetic resonance-guided focused ultrasound (MRgFUS) to pinpoint deeply located pharmacological targets while safeguarding the surrounding healthy brain tissue [19,20]. In contrast to osmotic disruption, which impacts large vascular areas, FUS, especially when paired with microbubbles, achieves a localized and temporary opening in the barrier [21]. This disruption is reversible; the BBB generally re-establishes its integrity within 6 to 24 hours following sonication, providing a dependable "therapeutic window" for drug delivery without causing enduring neurovascular damage [22,23].

Additionally, this method is "agnostic" regarding the therapeutic agents employed. It has proven effective in delivering a range of substances that typically struggle to penetrate the CNS, including small-molecule chemotherapeutics such as doxorubicin [24] and larger biologics like monoclonal antibodies (such as trastuzumab and aducanumab) [25,26]. Particularly relevant to contemporary formulation methods, FUS significantly improves the delivery and infiltration of nanoparticulate carriers (including liposomes and polymeric nanoparticles) and gene vectors, facilitating their passage across the BBB and their distribution throughout the brain interstitium [27]. This distinctive combination of being non-invasive, spatially precise, and versatile makes FUS an exceptionally promising technique for targeted drug delivery to the brain.

Following FUS-mediated BBB opening, nanoparticles can accumulate in brain tissue through passive accumulation or active targeting, each offering distinct advantages and limitations. Passive accumulation is mainly based on BBB permeability, which is increased through FUS, allowing nanoparticles to enter the brain based on size, surface charge, and circulation time. While this approach is relatively simple and generally applicable, it has limited control over cellular localization and may result in a heterogeneous distribution and nonspecific uptake in brain tissue. In active targeting, surface-functionalized nanoparticles are conjugated with ligands such as transferrin, angiopep-2, antibodies, peptides, or aptamers that recognize BBB receptors and/or disease-specific cellular markers, facilitating selective uptake by target cells (e.g., neurons, glioma cells, and/or activated microglia), thereby enhancing therapeutic specificity and reducing off-target effects. While active targeting can be effective, it depends on receptor expression, ligand affinity, and nanoparticle design. Therefore, combining FUS-mediated BBB opening with active targeting strategies will provide a more effective combination of brain penetration and selective cell delivery and is a promising platform for precision CNS therapeutics.

Although FUS-mediated BBB opening is generally safe and reversible under optimal treatment conditions, there have been reported adverse effects depending on ultrasound parameters, microbubble dose, and cavitation pattern. Microhemorrhage, vasogenic edema, neuroinflammation, endothelial injury, neuronal damage, transient neurological symptoms, and long-term permeability of the BBB can arise if inertial cavitation occurs or if acoustic pressure is applied. Preclinical studies have demonstrated transient activation of microglia and astrocytes with a sterile inflammatory response after BBB opening, but early clinical trials have shown that MRgFUS leads to localized and reversible BBB-induced disruption with good safety when stable cavitation is maintained and real-time monitoring is used. There are still long-term clinical studies to examine the cumulative effects of repeated BBB opening and to establish a standard treatment protocol for routine clinical use.

FUS-mediated BBB opening has been shown to be safe in preclinical and early clinical studies, but its biological effects are to be considered in the long term. Repeated BBB opening has been associated with transient neuroinflammatory effects such as activation of microglia and astrocytes and elevated levels of pro-inflammatory cytokines. Exposure to too much ultrasound or uncontrolled inertial cavitation can also induce oxidative stress, endothelial dysfunction, and microvascular damage, including petechial hemorrhage and disruption of cerebral capillaries. These are generally reduced when cavitation is maintained with appropriate acoustic parameters and cavitation monitoring in real time. Studies show that repeated FUS treatments do not result in long-term neuronal loss or persistent cognitive impairment under certain treatments. The clinical trials in patients with Alzheimer's disease, glioblastoma, and other neurological disorders have shown reversible BBB opening without significant deterioration of cognitive or neurological function, although patient numbers and follow-up periods are limited. However, in order to test the long-term safety of FUS-assisted brain drug delivery, it is necessary to continue to investigate the long-term effects of BBB disruption on chronic neuroinflammation, oxidative damage, vascular remodeling, and cognitive outcomes.

4. Principles of the Tri–Component System [Focused Ultrasound (FUS) and Microbubble (MB) Cavitation]

The fundamental biophysical process that results in FUS-induced changes to the BBB relies on the acoustic excitation of intravascular microbubbles (MBs), converting these inert gaseous carriers into active mechanical elements [28,29]. Generally, these microbubbles, ranging in size from 1 to 8 μm in diameter to facilitate transpulmonary movement, are composed of a high-molecular-weight gas core (such as perfluorocarbon or sulfur hexafluoride) surrounded by a stabilizing shell made of lipid, protein, or polymer [30,31]. The significant difference in density and compressibility between the gas core and the surrounding blood plasma—a phenomenon referred to as acoustic

impedance mismatch—enables MBs to serve as highly effective resonant scatterers of ultrasound waves [32,33].

When subjected to the alternating phases of compression and rarefaction within a focused ultrasound setting, the MBs experience acoustic cavitation, an oscillatory behavior that can be classified into two pressure-dependent phases [34]. At lower peak-negative pressures (typically between 0.3 and 0.6 MPa), MBs enter a stable (non-inertial) cavitation phase [35]. In this state, the bubbles continuously change in volume around their equilibrium size without collapsing [36]. This stable oscillation represents the ideal therapeutic "sweet spot", as it produces beneficial fluid dynamic effects—specifically acoustic microstreaming (steady fluid movement) and shear stress—that mechanically energize the endothelial cytoskeleton and stretch junctions [37,38,39]. The acoustic features associated with stable cavitation are characterized by the release of subharmonic and ultraharmonic frequencies in relation to the primary driving frequency [40,41].

In contrast, at higher acoustic pressures, MBs shift into inertial (transient) cavitation [42]. During this phase, the bubble expands to a critical threshold before collapsing abruptly, driven by the inertia of the surrounding liquid. This implosion generates high-energy effects, including localized shockwaves, extreme temperatures, and rapid liquid microjets [43,44]. Although inertial cavitation can successfully disrupt the BBB, it is often linked to vascular injury, which may involve damage to the endothelial lining, leakage of red blood cells, and microhemorrhaging within the tissue [45,46]. To mitigate these risks, contemporary clinical systems employ passive acoustic mapping (PAM) to identify broadband emissions that signify inertial collapse and utilize closed-loop feedback mechanisms to maintain acoustic pressure within safe limits for stable cavitation [47].

Microbubble cavitation is the biological mechanism of FUS engagement of BBB opening, which can be divided into stable (non-inertial) cavitation and inertial (transient) cavitation with different biological impacts. Stable cavitation occurs at relatively low acoustic pressures, where microbubbles are continuously expanding and contracting without collapsing. These movements produce acoustic microstreaming, shear stress, and muscular force-induced fluctuations that stimulate endothelial cells, cause local reorganization of the cytoskeleton, and then disrupt tight junction proteins like claudin-5, occludin, and zonula occludens-1 (ZO-1) and facilitate local BBB opening. The process results in high-energy shock waves, liquid microjets, localized heating, and free radical formation, resulting in significant increases in vascular permeability but also in significantly higher endothelial disruption, erythrocyte extravasation, petechial hemorrhage, vasogenic edema, and neuroinflammatory reactions. Inertial cavitation may improve drug penetration in some clinical applications; however, uncontrolled cavitation is a serious hazard and limits the application of the therapy. That is why MRgFUS platforms now rely on passive cavitation detection (PCD), acoustic emissions monitoring, and real-time closed-loop feedback systems to detect the harmonic and ultraharmonic signals related to stable cavitation and to minimize broadband emissions related to inertial cavitation. These methods of monitoring ultrasound parameters and the acoustic emissions are used to optimize BBB opening with minimal adverse biological effects [45,46,47].

5. Mechanism of BBB Disruption

The transient opening of the BBB by FUS in the presence of circulating microbubbles is a careful biomechanical process that promotes endothelial cell interaction by cavitation and does not destroy the tissue. When exposed to low-intensity pulsed ultrasound, the microbubbles oscillate in the brain capillaries, resulting in stable cavitation, which remains continuous and does not collapse [19,32]. This oscillating activity is accompanied by localized shear stress, acoustic microstreaming, and circumferential forces that physically stimulate the endothelial cells while preserving vascular integrity [35,38]. On the other hand, high acoustic pressure may cause inertial cavitation and violent microbubble collapse, which leads to shock waves and microjets that can cause endothelial damage, extravasation of erythrocytes, and microhemorrhage. The current clinical systems are based on real-time monitoring of cavitation and acoustic feedback to keep the cavitation stable and safe [48]. The mechanical stimulation of brain endothelial cells through stable cavitation leads to several mechanotransduction pathways in brain endothelial cells that can be activated by membrane tension and mechanosensitive ion channels, which induce transient intracellular calcium influx and cell remodeling and signaling pathways involving phosphorylation-dependent pathways [49,50]. This can lead to the reversible breakdown of the tight junction proteins, such as claudin-5, occludin, and ZO-1, and thus to the transient increase in permeability and the migration of the cell membrane [51]. In addition to this, FUS also increases the permeability of the cells through the formation of caveolae and vesicle transcytosis, facilitating the transport of larger molecules and nanoparticles across the endothelial barrier. In case of sensitive acoustic conditions, sonoporation may also promote permeability by forming nanoscale membrane pores that quickly reseal after treatment [52,53]. More importantly, BBB opening due to FUS and microbubbles is reversible and spatially limited. Tight junction proteins are slowly reassembled, endothelial integrity is restored, and normal BBB function can be restored within 6–24 hours, depending on ultrasound parameters, microbubble dose, and vascular profile. This short therapeutic window can be used to efficiently deliver small molecules, biologics, nucleic acids, and nanoparticle-based drug delivery systems with minimal neurovascular damage over the long term. An excellent understanding of these molecular and

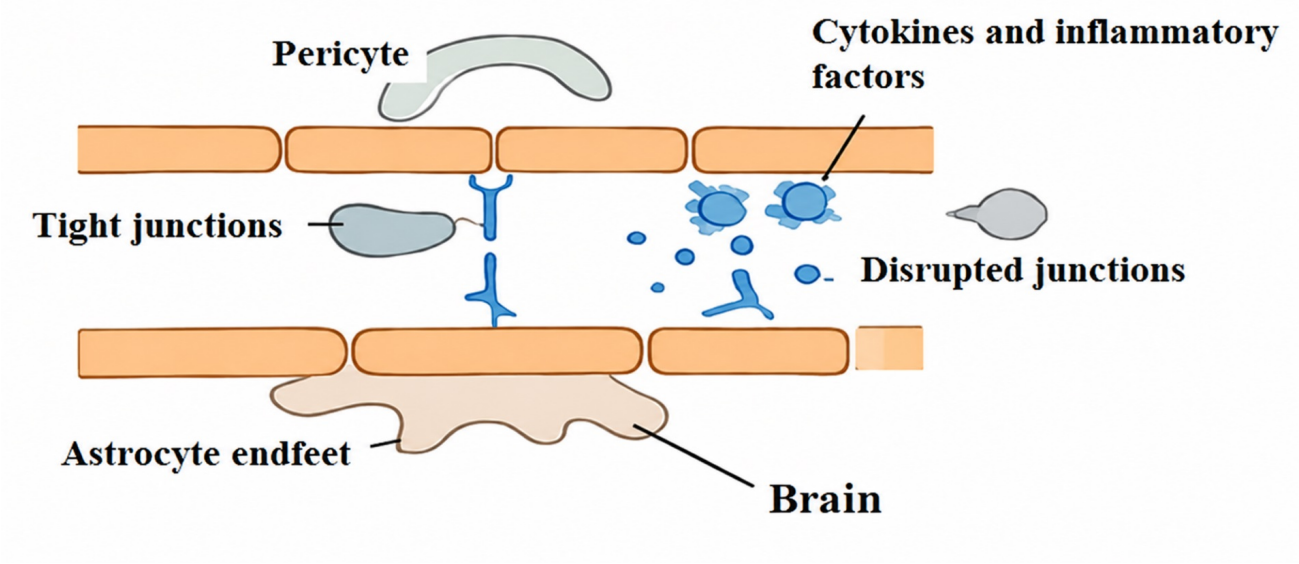


Fig. 1. Mechanism of blood–brain barrier (BBB) disruption. Inflammatory stimuli trigger the release of pro-inflammatory cytokines and other mediators, promoting endothelial dysfunction and oxidative stress. These processes alter tight-junction proteins, including claudin-5, occludin, and zonula occludens-1 (ZO-1), while matrix metalloproteinases contribute to the degradation of the basement membrane and associated barrier structures. Concurrently, increased endothelial transcytosis may facilitate the passage of circulating substances across the BBB. Collectively, these alterations disrupt the integrity of the neurovascular unit, increase BBB permeability, and promote the extravasation of plasma proteins and, under pathological conditions, immune cells into the brain parenchyma, thereby exacerbating neuroinflammation and neuronal dysfunction.

cellular mechanisms is needed to tailor treatment protocols to enhance therapeutic effectiveness and ensure safe clinical translation of FUS-mediated brain drug delivery [22]. Fig. 1 illustrates the structure and function of the blood–brain barrier (BBB), which regulates the movement of substances between the bloodstream and brain tissue. Tight junctions between endothelial cells restrict the entry of unwanted substances into the brain, while pericytes and astrocyte endfeet help maintain BBB integrity. However, cytokines and inflammatory factors can disrupt these tight junctions, increasing BBB permeability. This disruption may facilitate the entry of inflammatory mediators and other substances into the brain, potentially contributing to neuroinflammation and neurological disorders.

6. Nanoparticles (NPs) as Drug Delivery Vectors

Several research reports in preclinical studies have demonstrated the effectiveness of FUS BBB opening to improve brain drug delivery. In one of the most important studies, Treat et al. [54] reported that MR-guided focused ultrasound (MRgFUS)-assisted delivery of doxorubicin. Other studies have explored the use of FUS and microbubbles to improve liposomal doxorubicin delivery and the brain accumulation of engineered nanoparticles. These results clearly demonstrate that FUS greatly improves localized drug and nanocarrier delivery compared to untreated controls while maintaining a favorable safety profile under optimized treatment conditions [45,55].

Recent progress in nanoparticle design has led to the development of multifunctional nanocarriers that can overcome the biological barriers to CNS drug delivery. Ligand-based nanoparticles with targeting molecules (transferrin, angiopep-2, lactoferrin, antibodies, peptides, aptamers) can enhance receptor transcytosis in the BBB and enhance selective uptake in disease-ridden brain cells. Biomimetic nanoparticles such as cell membrane-coated nanoparticles and extracellular vesicle-based nanocarriers are able to access biological interfaces to avoid immune rejection, prolong circulation, and target tissues. Among these systems, exosomes have emerged as promising endogenous nanocarriers due to their biocompatibility, low immunogenicity, and ability to transport proteins, nucleic acids, and small molecules across biological boundaries. Furthermore, hybrid nanocarriers incorporate polymeric, lipid, inorganic, or biological components to achieve improved drug loading, controlled release, and targeting efficiency. Stimuli-responsive nanoparticles, which respond to internal stimuli (pH, enzymes, redox potential) or external stimuli (ultrasound, magnetic fields, or light), allow the release of drugs in space and time at a controlled level. When coupled with FUS-induced transient BBB opening, these innovative nanoparticle engineering strategies provide the possibility to achieve complementary advancement of brain penetration, cell targeting, therapeutic efficacy, and safety, which is of great potential for precision nanomedicine in neurological disorders.

7. Ultrasound Wave Responsive NP

Ultrasound-mediated drug delivery is a non-invasive technique that utilizes focused ultrasound waves to temporarily open the BBB and facilitate the transport of therapeutic drugs to the brain [56,57,58]. Ultrasound waves can function independently or in combination with microbubbles. These tiny gas-filled bubbles respond to the ultrasound waves, leading to mechanical disruption of the endothelial cells within the BBB [56,57]. Employing ultrasound in conjunction with NPs has demonstrated an enhancement in the delivery of therapeutic agents to the brain. NPs are capable of carrying drugs and assisting in their movement across the compromised BBB [56,58,59].

Low-frequency FUS presents a novel, non-invasive technique for temporarily and reversibly opening the BBB. Utilizing MRgFUS, this approach employs low-frequency ultrasound waves combined with gas-filled microbubbles to specifically target and disrupt the BBB [60]. The microbubbles, typically composed of lipid-encapsulated perfluorocarbon gas and measuring between 1 and 5 μm in diameter, are often employed as contrast agents in ultrasound imaging, aiding in the precise targeting and disruption of the BBB for therapeutic applications [61,62]. The pressure levels applied during FUS to facilitate BBB opening are safe for human use, aligning with those utilized in diagnostic ultrasound, specifically under 1.5–2 MPa. Although the precise mechanisms through which FUS opens the BBB remain unclear, it is thought that ultrasound waves lead to microbubble interactions with adjacent brain tissue primarily via two processes: stable and inertial cavitation. Stable cavitation occurs when microbubbles oscillate in a low-pressure context, creating microstreaming in surrounding fluid and exerting mechanical forces on endothelial cells that temporarily disrupt tight junction proteins [63]. In contrast, inertial cavitation, which occurs under high-pressure conditions, causes microbubbles to collapse or fragment, generating powerful forces such as shock waves and microjets that can damage cell membranes and enhance the permeability of blood vessels [64].

Liposomes are among the most extensively studied NPs used in collaboration with ultrasound. These spherical vesicles, formed from a lipid bilayer, can encapsulate both hydrophilic and hydrophobic drugs. This distinctive structure enables them to serve as versatile carriers for a variety of therapeutic agents. When combined with ultrasound, liposomes can be administered quickly and non-invasively to the brain, significantly improving drug delivery efficiency and therapeutic outcomes [65,66]. For glioma treatment, a method known as magnetic resonance image-guided microbubble-enhanced low-intensity pulsed focused ultrasound (LIFU) is utilized to temporarily open the BBB [67]. This technique facilitates the delivery of a novel liposome-encapsulated small molecule, specifically an O^6-methylguanine-DNA methyltransferase (MGMT) inhibitor, to mice afflicted with temozolomide-resistant gliomas, underscoring the potential of integrating liposomal drug carriers for more effective targeting and treatment of challenging brain tumors [68].

In addition to liposomes, various other nanoparticles, including polymeric NPs and dendrimers, have been investigated for their ability to enhance BBB permeability using ultrasound. Polymeric NPs are constructed from biocompatible polymers like poly(lactic-co-glycolic acid) (PLGA) or polyethylene glycol (PEG), allowing for the design of tailored carriers that can encapsulate different drugs aimed at specific cells or tissues [69]. The application of ultrasound alongside polymeric NPs has demonstrated improved delivery of therapeutic agents to the brain, resulting in more favorable treatment outcomes [70].

The combination of ultrasound and NPs for achieving BBB permeabilization offers numerous advantages compared to alternative methods. Primarily, ultrasound is a non-invasive and safe approach that can be directed at the target area without causing damage to surrounding tissues [71]. Additionally, NPs can be engineered to selectively target particular cells, enabling concentrated delivery of therapeutic agents to the brain [56]. Lastly, the integration of ultrasound with NPs can enhance the efficiency of therapeutic agent delivery to the brain, leading to improved treatment results [64].

Despite the promising potential of ultrasound-mediated drug delivery, several obstacles remain to be addressed for wider clinical application. A key challenge lies in precisely calibrating the ultrasound parameters to ensure sufficient BBB disruption while avoiding damage to tissue or eliciting an immune response. Another difficulty involves ensuring that therapeutic agents appropriately target the tumor site to prevent detrimental effects on healthy brain tissue [58,59].

Recent developments in ultrasound technology, including advancements in high-frequency ultrasound and real-time imaging methods for monitoring drug delivery, hold promise for alleviating some of these challenges. Ongoing research aims to investigate the possibilities of employing ultrasound-mediated drug delivery in conjunction with other therapies, such as immunotherapy, to enhance the efficacy of glioblastoma treatment [57,59].

8. Magnetic Field Responsive NP

Magnetic targeting and guidance represent a non-invasive approach that employs magnetic fields to navigate magnetic nanoparticles (MNPs) toward glioblastoma (GBM) locations. This method is based on magnetic nanoparticles that can carry therapeutic agents and can be maneuvered through an external magnetic field into GBM tissues across the BBB [72,73]. Prior to systemic administration, these MNPs are associated with therapeutic molecules. After being injected into the bloodstream, they travel until an external magnetic field is applied at the GBM site [72,73,74]. This external magnetic field serves as a fo-

cal point, attracting the MNPs into the brain tumor, which can markedly increase local drug concentrations and enhance therapeutic efficacy [75]. To ensure stability during circulation and minimize immune recognition, these MNPs are typically coated with biocompatible materials that prevent early opsonization or aggregation in the vascular system [76]. When the magnetic field directs these MNPs toward the brain tumor, they facilitate the swift delivery of therapeutic agents, thus elevating drug concentrations at the target location while decreasing systemic exposure [72,74].

Magnetic resonance imaging (MRI) is a key component of FUS-mediated BBB opening, allowing for accurate treatment planning, focused targeting, real-time monitoring, and post-treatment evaluation. MRI imaging prior to sonication can help identify the target region, avoid critical neurovascular structures, and optimize ultrasound parameters based on patients' anatomy. MRI guidance helps to ensure a precise focal alignment during treatment and can be incorporated into acoustic feedback systems for targeting accuracy and procedural safety. After sonication, contrast-enhanced T1-weighted MRI can be used to confirm the extent and location of BBB opening, and T2- and susceptibility-weighted imaging (SWI) are employed to detect potential adverse effects, including edema or microhemorrhage. This imaging approach enables quantitative assessment of BBB permeability, verification of treatment accuracy, and monitoring of BBB recovery, which is essential in terms of safety, reproducibility, and clinical translation of MRgFUS to CNS drug delivery [73,74].

Superparamagnetic iron oxide nanoparticles (SPIONs) possess unique magnetic characteristics due to their iron oxide core and the enclosing polymer coating. This configuration not only imparts magnetic responsiveness to SPIONs but also secures essential biological traits such as biocompatibility, internalization, and viability [77]. Leveraging these magnetic features, an innovative treatment strategy employs an external magnetic field to specifically target SPIONs to tumor sites. One study investigated the administration of SPIONs bonded to the chemotherapy drug temozolomide (TMZ) for GBM treatment. The SPIONs-TMZ combinations were able to cross the BBB and accumulate at the tumor location, resulting in improved efficacy compared to unbound TMZ [78]. However, despite these advancements, magnetic targeting faces several challenges and limitations. The introduction of a magnetic field within body tissues can inadvertently increase temperature, a phenomenon known as magnetic hyperthermia, which may harm healthy adjacent tissues [79]. Furthermore, there is a possibility that MNPs could disseminate to unintended organs or tissues, leading to undesirable side effects. To mitigate these risks, it is essential to optimize the power and exposure duration of the magnetic field carefully [80]. A comprehensive understanding of the MNPs' physical and chemical attributes—such as magnetic responsiveness, size, surface charge, and biodegradability—is crucial, as these parameters greatly affect the MNPs' circulation time, body distribution, and targeting accuracy [73,81].

As investigations progress, there is a growing emphasis on developing sophisticated MNP systems that provide controlled drug release, targeted delivery, and minimal off-target accumulation [82]. This entails the incorporation of stimulus-responsive elements into the MNP design, enabling the controlled release of drugs based on particular signals at the tumor site [72]. Magnetic field techniques for traversing the BBB offer both advantages and disadvantages that are relevant for clinical applications [73,79,80]. A significant benefit is the non-invasive nature of the method, which renders it safer and more comfortable for patients. It allows for the remote activation of drug release, furnishing precise control over when and where the drug exerts its effect [79]. Moreover, concentrating the magnetic nanoparticles within the brain reduces systemic side effects, leading to a more focused treatment that disrupts other bodily systems less [80]. Nevertheless, the limitations of this technique must be acknowledged. It is only applicable to a restricted array of drugs that are compatible with magnetic nanoparticles. The extent to which the magnetic field can penetrate brain tissue is limited, which may decrease its efficiency for deeper brain areas. Additionally, utilizing high-intensity magnetic fields raises worries about potential tissue heating and damage, endangering patient safety [79,80]. Therefore, although magnetic field approaches provide a promising pathway for crossing the BBB, their implementation must be meticulously weighed against these intrinsic limitations.

9. Viral Vector Drug Delivery

9.1 Virus-Like NP

Virus-like nanoparticle (VLP) drug delivery has surfaced as a highly promising strategy for treating glioblastoma (GBM), primarily due to its ability to effectively penetrate the BBB. VLPs resemble viruses in structure but lack viral genetic material. They present a novel method for transporting therapeutic agents across the BBB to target GBM cells [83]. VLPs are recognized for their structural resemblance to viruses, enabling them to utilize the natural pathways that viruses leverage for cellular entry, without the dangers of viral replication or infection [83,84]. This characteristic makes VLPs a compelling option for drug delivery, as they can accommodate various therapeutic agents, including small molecules, nucleic acids, and proteins [83]. Recent studies have concentrated on understanding the intricate mechanisms that viruses employ to navigate the BBB [84].

Research indicates that SARS-CoV-2 can impact multiple cranial nerves, including the olfactory, trigeminal, optic, and vagus nerves. Additionally, following a typical respiratory infection, SARS-CoV-2 can disseminate into the systemic circulatory system. Upon reaching the BBB, SARS-CoV-2 can infiltrate endothelial cells through its in-

teraction with the angiotensin-converting enzyme 2 (ACE2) receptor, changes in the tight junction proteins comprising BBB endothelial cells, or through phagocytosis by immune cells. The routes of entry include transcellular pathways, paracellular pathways, and the Trojan horse pathway [85]. The entry of John Cunningham virus-like particles (JC VLPs) into brain endothelial cells involves clathrin-dependent mechanisms. *In vitro* experiments have demonstrated exocytosis and both cellular and paracellular transcytosis of VLPs through the BBB. Researchers observed VLPs within mouse brain endothelial cells following intravenous (IV) and internal carotid artery (ICA) injections [86].

The capability of VLPs to traverse the BBB is crucial for their efficacy in treating GBM. Investigators are examining various approaches to enhance BBB penetration, such as altering the surface characteristics of VLPs to leverage receptor-mediated transcytosis mechanisms [87]. The exploration of VLPs for the treatment of brain tumors is still in its nascent phases; however, it shows potential given that various viruses capable of crossing the BBB have been recognized [88].

Ensuring the safety and compatibility of VLPs is vital for their application in clinical settings. Although VLPs hold great promise for GBM treatment, obstacles persist in transitioning these technologies from research laboratories to clinical environments. Factors such as the scalability of VLP production, the stability of drug encapsulation, and the long-term safety of these delivery systems need thorough examination. Continuous research and clinical trials are essential to fine-tune VLP technology, assess its effectiveness in treating GBM, and ultimately incorporate VLP-based drug delivery into standard GBM treatment protocols [84].

9.2 Intranasal NP Drug Delivery

Intranasal administration is an attractive and non-invasive approach for delivering medications to the brain. The olfactory and trigeminal nerves located in the nasal cavity provide direct access to the brain, circumventing the BBB [89,90]. Furthermore, intranasal delivery is a straightforward and painless method for administering medications, making it especially useful for long-term or repeated treatments. However, this method primarily accommodates small molecules and lipophilic drugs, which restricts the range of medications that can be delivered effectively. Researchers have explored the use of NPs to enhance the intranasal delivery of drugs to the brain [91,92].

The initial phase of utilizing NPs for nasal drug administration involves delivering them as a nasal spray or droplets. Once administered intranasally, the NPs distribute throughout the nasal cavity. The extensive surface area and abundant blood supply of the nasal mucosa facilitate the absorption of drugs [91]. The NPs can settle in different regions of the nasal cavity, such as the olfactory region and the respiratory region. The olfactory region is particularly significant for drug delivery to the brain, as it provides a direct route through the olfactory epithelium and associated nerves. Although the olfactory epithelium is less rigid than the cerebral blood–brain barrier and allows for partial nose-to-brain drug transport, it is restricted by mucus clearance, enzymatic degradation, and reduced diffusion in the olfactory and trigeminal pathways. On the other hand, FUS-mediated drug delivery is designed to open the BBB of the brain in a transient and localized fashion with microbubble-assisted cavitation and therefore to deliver drugs to specific brain regions. In addition, there is no clear evidence that FUS can further increase drug transport in the olfactory epithelium itself. Therefore, intranasal delivery and FUS-mediated BBB opening should be viewed as complementary and not as overlapping strategies for CNS drug delivery.

The NPs can directly access the olfactory bulb and then disperse into other areas of the brain. In the respiratory region, the NPs have the potential to enter the bloodstream and subsequently reach the brain via systemic circulation [91,92]. After settling in the nasal cavity, the NPs interact with the nasal mucosa. The surface properties of the NPs play a crucial role in determining their interactions with the mucosal tissues. NPs can traverse the nasal mucosa through various mechanisms, including diffusion, endocytosis, and paracellular or transcellular transport [93]. Thanks to their small size and advantageous characteristics, the NPs can move across nasal epithelial cells. Furthermore, certain NPs can be taken up by nasal epithelial cells through endocytosis, allowing them to bypass the mucosal barrier and enter the bloodstream [93,94].

NP-mediated intranasal delivery has demonstrated improved brain delivery of medications that struggle to cross the BBB. Polymeric NPs, such as PLGA and chitosan, have been employed to enhance the intranasal delivery of diverse drugs to the brain. Solid lipid NPs (SLNs) have also been investigated for intranasal drug delivery, as they can enhance drug solubility and stability while promoting drug transport across the nasal mucosa. NP-based intranasal drug delivery offers prompt therapeutic action due to direct access to the brain and quick absorption through the well-vascularized mucosa, resulting in rapid therapeutic effects. Additionally, it is user-friendly and may be effective for low molecular weight drugs, improving their bioavailability. However, this method has significant limitations. It is only appropriate for a specific range of drug types, and the rapid mucociliary clearance in the nasal cavity may lead to quick removal of the medication [89,90]. There is also a chance of losing part of the dose due to improper administration. Some patients may experience nasal irritation or discomfort, and there is a limit to the quantity of drug that can be effectively delivered through this method. These factors make it imperative to balance the advantages and disadvantages of intranasal drug delivery for conditions

like glioblastoma. Further research is necessary to refine NP systems for intranasal drug administration and evaluate their effectiveness and safety in clinical applications [91].

10. Recent Advances in FUS–Microbubble–Nanoparticle System

Recent advances in the FUS–microbubble–nanoparticle system have significantly improved the efficiency and precision of brain drug delivery by overcoming the restrictive nature of the BBB. MRI-guided FUS combined with circulating microbubbles has emerged as a noninvasive technique capable of producing temporary and localized BBB disruption with high spatial accuracy. Improvements in microbubble formulation and cavitation control have enhanced the safety, stability, and reproducibility of BBB opening, thereby minimizing damage to healthy brain tissues. Simultaneously, real-time imaging technologies have enabled accurate monitoring of BBB permeability and therapeutic distribution during treatment.

In parallel, major progress has been achieved in nanoparticle engineering for targeted central nervous system delivery. Polymeric, lipid-based, and surface-functionalized nanoparticles have been developed to improve drug stability, brain penetration, and selective cellular uptake. FUS-mediated BBB opening has been shown to be a promising approach to non-invasive delivery of nucleic acid drugs such as siRNA, mRNA, plasmid DNA, antisense oligonucleotides (ASOs), and CRISPR/Cas gene editing, which are usually poorly permeable and rapidly degraded by the BBB system. Encapsulation within lipid nanoparticles, polymeric nanoparticles, or other nanocarriers protects these molecules from nuclease degradation, improves circulation, and enhances intracellular delivery after transient BBB opening. This approach is thus capable of silencing genes, protein replacement, genome editing, and modulation of disease-associated pathways in neurological disorders. Recently, it has been shown that FUS and nanoparticle-based carriers are very effective in brain delivery of siRNA and mRNA, and CRISPR/Cas systems can be delivered to the brain for gene editing and to enhance system-level genome editing at a low systemic exposure. These findings have great potential for brain tumors, Alzheimer's disease, Parkinson's disease, Huntington's disease, and other genetic neurological disorders. However, further optimization of delivery efficiency, editing specificity, long-term safety, and immunogenicity is needed before widespread clinical translation is possible. These nanocarriers can encapsulate a wide range of therapeutic agents, including chemotherapeutics, proteins, genes, siRNA, and CRISPR-based systems, while also providing sustained and controlled drug release. Multifunctional nanoparticles integrated with targeting ligands and imaging agents have further enhanced theranostic applications by combining diagnosis and therapy within a single platform [90,91].

Surface functionalization has been shown to be a promising means of targeting nanoparticles in an efficient manner following FUS-mediated BBB opening. Nanocarrier targeting can be achieved by conjugating nanoparticles to BBB-associated receptors (transferrin receptor (TfR), low-density lipoprotein receptor-related protein 1 (LRP1), insulin receptor, and LDL receptors) to promote receptor-mediated endocytosis and transcytosis in brain endothelial cells. In addition to facilitating BBB transport, these ligands lead to accumulation in diseased brain tissues and decrease the systemic distribution of non-cancerous molecules. In addition to targeted targeting of BBB-associated receptors, surface-functionalized nanoparticles can be customized for cell uptake by the use of antibodies, peptides, aptamers, and cell membrane-based coatings, as they can recognize neurons, glioma cells, activated microglia, or other pathogens. Surface modification such as PEGylation also enhances colloidal stability and prolongs circulation, and multi-targeting nanocarrier devices integrating targeting ligands and imaging or therapy can be applied at the same time. When combined with transient BBB opening caused by FUS, these active targeting strategies have the potential to rapidly build drug accumulation at the desired site, enhance therapeutic effectiveness, decrease off-target toxicity, and to develop precision nanomedicine for central nervous system disorders.

Recent preclinical and early clinical studies have demonstrated the potential of this triad-based approach in the treatment of glioblastoma, Alzheimer's disease, Parkinson's disease, epilepsy, stroke, and neuroinflammatory disorders. The integration of artificial intelligence, precision imaging, and personalized nanomedicine strategies has further accelerated the translation of this technology toward clinical practice. Overall, the FUS–microbubble–nanoparticle system represents a promising advancement in modern neurotherapeutics, offering safer, site-specific, and more effective treatment options for complex neurological diseases. Table 1 (Ref. [14,15,27,58,64,65,66,67,68,86,87,88,95,96,97,98,99,100]) presents recent advances in the FUS–microbubble–nanoparticle system.

The therapeutic effect of FUS-mediated BBB opening is very much dependent on the parameters of ultrasound. The frequency varies with the depth of penetration and focal accuracy, and lower frequencies (typically 220–700 kHz) are preferred in transcranial applications by reducing skull attenuation. The pressure of the acoustic probe is the most important parameter for microbubble cavitation and must be high enough to create stable cavitation without inertial cavitation and vascular damage. The pulse duration, pulse repetition frequency, and exposure time also impact the amount of BBB opening and the duration, with shorter pulsed exposure typically leading to the removal of BBB and better safety. These parameters should be optimized with microbubble dose and cavitation

Table 1. Representative nanoparticle systems for FUS-mediated CNS drug delivery.

Nanoparticle system	Composition	Typical size (nm)	Therapeutic cargo	Major advantages	Limitations	Representative CNS applications	Reference
Polymeric nanoparticles	PLGA, PLA, PEG-PLGA, chitosan	50–250	Small molecules, proteins, siRNA, DNA	Controlled release, high stability, surface functionalization	Moderate drug loading, polymer degradation	Glioblastoma, Alzheimer's disease, Parkinson's disease	[27,58,64,97]
Lipid nanoparticles (LNPs)	Ionizable lipids, phospholipids, cholesterol	50–150	mRNA, siRNA, CRISPR/Cas cargo	High nucleic acid encapsulation, clinical translation	Limited stability, hepatic uptake	Gene therapy, neurodegenerative disorders	[66,98,99]
Liposomes	Phospholipid bilayers	80–300	Hydrophilic and lipophilic drugs	Excellent biocompatibility, clinical experience	Drug leakage, short circulation without PEGylation	Brain tumors, stroke	[65,67,68]
Polymeric micelles	PEG-PCL, PEG-PLA	20–100	Hydrophobic drugs	Improved solubility, prolonged circulation	Lower structural stability	Brain tumors	[14,15,100]
Dendrimers	PAMAM, PPI	5–30	Drugs, genes, imaging agents	High loading capacity, multivalent surface	Possible cytotoxicity (cationic)	Neuroinflammation, glioma	[14,15,100]
Biomimetic nanoparticles	Cell membrane-coated nanoparticles, extracellular vesicles	50–200	Drugs, proteins, RNA	Immune evasion, prolonged circulation, enhanced targeting	Complex manufacturing	Brain tumors, neurodegeneration	[86,87,88,95,96,100]

FUS, focused ultrasound; CNS, central nervous system; PLGA, poly(lactic-co-glycolic acid); PLA, poly(lactic acid); PEG-PLGA, poly(ethylene glycol)-poly(lactic-co-glycolic acid); PEG-PCL, poly(ethylene glycol)-poly(ε-caprolactone); PEG-PLA, poly(ethylene glycol)-poly(lactic acid); PAMAM, poly(amidoamine); PPI, poly(propylene imine); PEG, polyethylene glycol; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; mRNA, messenger RNA; siRNA, small interfering RNA; CRISPR, clustered regularly interspaced short palindromic repeats; Cas, CRISPR-associated protein.

in real time (as a means to achieve maximum dose and low effects of edema, microhemorrhage, and neuroinflammation). MRgFUS systems combined with passive cavitation detection allow for individualized parameter adjustment, which in turn improves targeting accuracy and reproducibility, and clinical safety. In addition, standardization of ultrasound exposure protocols is an important step toward the successful clinical translation of FUS-mediated CNS drug delivery [90,91]. The key ultrasound parameters affecting the efficacy and safety of BBB opening, including frequency, acoustic pressure, pulse duration, pulse repetition frequency, and sonication time.

Although FUS-mediated BBB opening has shown a good safety profile in preclinical and early clinical studies, the safety is largely determined by the appropriate ultrasound parameters and microbubble administration. If too much acoustic pressure or uncontrolled inertial cavitation is present, microhemorrhage, endothelial damage, vasogenic edema, neuronal injury, and short-term neuroinflammatory activity will occur, and the therapeutic impact will be limited. Neuroinflammation is mainly caused by temporary activation of microglia and astrocytes and the release of inflammatory mediators, which will largely be restored to the BBB once BBB integrity is restored. Current MRgFUS systems with passive cavitation detection and real-time acoustic feedback can be used to control cavitation activity and reduce the risk of tissue injury while still allowing BBB opening. BBB damage is generally localized, reversible, and well tolerated, with restoration of BBB integrity within hours to days of treatment. However, longitudinal studies would be required to assess the potential long-term effects of repeated BBB opening, including cumulative neurovascular changes and cognitive effects, in order to ensure safe clinical translation of this technology.

11. Applications in Neuro-Oncology (e.g., Glioblastoma)

Microbubble-enhanced focused ultrasound (MB-FUS) represents a novel strategy in the treatment of glioblastoma (GBM), tackling significant issues such as the BBB and the tumor's immunosuppressive microenvironment [101]. GBM is the most prevalent and aggressive form of malignant glioma, with a median survival rate of under 18 months despite improvements in surgery, radiotherapy, and chemotherapy [102]. The BBB, which serves as a highly selective neurovascular barrier, hinders most therapeutic agents from effectively reaching the brain, thus limiting treatment effectiveness [103]. MB-FUS has emerged as a promising method to breach this barrier, facilitating transient and localized opening of the BBB through the interaction of sound waves with microbubbles injected into the bloodstream [101]. These microbubbles vibrate when exposed to ultrasound, causing mechanical disruption of endothelial tight junctions and enabling therapeutic agents to infiltrate brain tissue [19].

In brain tumors, FUS improves the delivery of chemotherapeutics, immunotherapeutics, and nanomedicines to tumor regions by overcoming heterogeneous BBB permeability. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, the transient BBB opening enables the delivery of antibodies, neurotrophic factors, and disease-modifying drugs while promoting the clearance of pathological protein aggregates. In stroke, FUS may help to better target the delivery of neuroprotective and regenerative drugs, but treatment timing and the risk of hemorrhagic transformation are important. In epilepsy, local BBB opening is possible to deliver antiseizure drugs with fewer systemic adverse effects. In gene therapy, FUS allows the non-invasive delivery of viral vectors, plasmid DNA, mRNA, siRNA, and CRISPR/Cas-based therapeutics, which is considered a promising approach to precision treatment of inherited and acquired neurological disorders. Presenting these effects in their own sections shows the different therapeutic potential, challenges, and future directions for each neurological disease.

One major use of MB-FUS in GBM is to enhance drug delivery [104]. Research has shown that MB-FUS can greatly enhance the delivery of small molecules, nanoparticles, and even adoptive immunotherapy approaches like chimeric antigen receptor (CAR)-T cells [105]. For example, MB-FUS has been demonstrated to boost the uptake and retention of temozolomide (TMZ), the standard chemotherapy for GBM, within the tumor area, thereby slowing tumor progression and prolonging survival in preclinical studies [106]. Moreover, microbubble-mediated focused ultrasound (MB-FUS) has demonstrated considerable potential in enhancing drug delivery across the blood–brain barrier (BBB), enabling the transport of therapeutic agents that would otherwise exhibit limited brain penetration, including carboplatin and doxorubicin [107].

Nanomedicines, such as liposomal, polymeric, and peptide-encapsulated therapies, have also benefited from MB-FUS, as the technology allows for controlled and sustained drug release, enhancing antitumor efficiency [108]. Additionally, MB-FUS has been investigated for delivering drug-loaded microbubbles, which can directly transport chemotherapy agents to the tumor, reducing off-target toxicity and improving treatment results [109].

In addition to drug delivery, MB-FUS has paved the way for advances in liquid biopsy (LBx) for GBM [110]. The BBB usually blocks tumor-related DNA and biomarkers from entering the bloodstream, limiting the capability of LBx for diagnosing and monitoring brain tumors [111]. The BBBO induced by MB-FUS has been shown to elevate plasma levels of tumor-specific biomarkers and circulating tumor DNA, thus facilitating more effective disease detection, treatment direction, and monitoring of residual disease [112]. This method has been confirmed in preclinical in-

Table 2. Applications of FUS–microbubble–nanoparticle system.

Application area	Application of FUS–microbubble–nanoparticle system	Key benefits	Reference
Brain tumor therapy	Targeted delivery of anticancer drugs across the BBB	Enhanced tumor targeting and reduced systemic toxicity	[104,105]
Alzheimer's disease	Delivery of antibodies and neuroprotective agents	Reduction of amyloid plaques and improved cognitive outcomes	[117,118]
Parkinson's disease	Transport of dopamine-related therapeutics and growth factors	Improved neuronal recovery and symptom control	[119,120]
Gene therapy	Delivery of siRNA, mRNA, plasmids, and CRISPR systems	Efficient gene modulation and sustained therapeutic action	[120,121,122,123,124]
Epilepsy treatment	Localized administration of antiepileptic drugs	Improved seizure management with fewer side effects	[127]
Stroke therapy	Delivery of neuroregenerative and neuroprotective agents	Enhanced brain tissue repair and functional recovery	[128]
CNS infections	Enhanced penetration of antimicrobial agents into the brain	Improved treatment efficacy against resistant infections	[131]
Neuroinflammatory disorders	Targeted delivery of anti-inflammatory therapeutics	Reduced neuroinflammation and neuronal damage	[125,126]
Brain imaging and diagnostics	Use of theranostic nanoparticles with MRgFUS	Simultaneous diagnosis and therapy monitoring	[129]
Precision medicine	Personalized and site-specific brain drug delivery	Safer, controlled, and patient-tailored treatment approach	[58,64,100,130]

BBB, blood–brain barrier; MRgFUS, magnetic resonance-guided focused ultrasound.

vestigations and early clinical trials, showing its safety and effectiveness.

MB-FUS also offers potential for modulating the immune system in GBM therapy [113]. By inducing mild and temporary neuroinflammation, MB-FUS can transform the immunosuppressive tumor environment into one that supports immune activation, thus enhancing immune surveillance and improving the effectiveness of immunotherapies like anti-PD1 and CAR-T cells [114]. Furthermore, MB-FUS has been studied for sonodynamic therapy (SDT), employing sonosensitizing agents that are activated by ultrasound to selectively target glioblastoma cells. This method has yielded promising outcomes in preclinical models, demonstrating enhanced therapeutic effectiveness and minimal damage to adjacent brain tissue [115].

While MB-FUS has shown considerable promise in preclinical research, clinical trials are currently underway to assess its safety, feasibility, and therapeutic advantages for patients with GBM, particularly in post-surgical contexts to prevent recurrence and improve adjuvant therapies. As MB-FUS technologies advance, standardizing treatment protocols and developing preclinical models that accurately replicate clinical scenarios will be critical for successful integration into standard clinical practice [116]. With continued progress, MB-FUS has the potential to transform GBM treatment and significantly enhance patient outcomes. The applications were summarized in Table 2 (Ref. [58,64,100,104,105,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131]).

12. Applications in Neurodegenerative Disorders

12.1 Alzheimer's Disease

Raymond et al. [129] successfully applied FUS-BBBO to enhance the penetration of both therapeutic and imaging drugs in AD animal models. Subsequently, Jordão et al. [26] showed that targeted transport of BAM-10 anti-betaamyloid antibodies induced a rapid clearance of plaque pathology in an AD mouse model. These results are consistent with those reported by Burgess et al. [117]; in that study, they focused on the hippocampus. The benefits on behavior were associated with a reduction of amyloid plaques and signs of neurogenesis in the hippocampus. Leinenga and Götz [118] demonstrated that repeated scanning ultrasound treatment was associated with a substantial reduction in amyloid plaque burden in approximately 75% of treated animals. This finding was supported by longitudinal imaging using a kinetic analysis approach and was attributed, at least in part, to the activation of microglia, suggesting a potential role for ultrasound-mediated modulation of neuroinflammatory responses in amyloid plaque clearance. Such reduction in plaques was correlated with memory and behavior performance improvement in the treated animals [118]. Another promising therapy target of both

AD and tauopathies is tauopathy. The combined use of FUS-BBBO and RN2N anti-tau antibodies was shown to specifically decrease phosphorylation levels of tau proteins and alleviate the anxiety-like behaviors [132]. Hsu and colleagues [133] demonstrated the effectiveness of inhibiting phosphorylation processes by using an advanced glycogen-synthase kinase-3 (GSK-3) inhibitor in an Alzheimer's disease (AD) animal model. This approach resulted in a significant reduction of amyloid plaques and a remarkable decrease in GSK-3 activity by as much as 61.3% [133]. Intravenous immunoglobulin (IVIg), which is derived from human blood and contains polyclonal antibodies, serves as an immunomodulator both in the periphery and centrally. Recent studies suggest that when FUS-BBBO is combined with increased IVIg deposition, it lowers the levels of the proinflammatory cytokine tumor necrosis factor (TNF)-alpha. This modulation of inflammatory responses not only promotes neurogenesis but also helps reduce amyloid plaques in the hippocampus of a transgenic AD animal model [134]. Given that impaired neurogenesis and the buildup of amyloid plaques are key features of AD, FUS-BBBO could be a promising strategy for enhancing treatment options.

12.2 Parkinson's Disease

The integration of low-intensity focused ultrasound (LIFU) with microbubbles (MBs) stands out as a feasible and highly promising therapeutic approach for Parkinson's disease (PD), allowing for the effective transportation of gene vectors to particular, targeted areas in the brain [135]. This method is crucial since the BBB often reduces the effectiveness of potential treatments like neurotrophic factors or agents aimed at α-synuclein [119,120]. The objective of utilizing this FUS-driven delivery is to promote neuroprotection, adjust protein expression, or even prevent the progression of conditions such as the spread of Lewy bodies. This therapeutic approach is being investigated using four main categories of gene vectors: DNA-loaded microbubbles, DNA-NPs, gene–liposome–MB complexes, and gene-adeno-associated virus (AAV) vectors.

The first category, DNA-loaded MBs, offers an innovative method of administration wherein the vector is attached directly to the microbubble. Research indicates that cationic microbubbles (cMBs) have a greater binding capacity for glial cell line-derived neurotrophic factor (GDNF) plasmids compared to neutral microbubbles, and a FUS-activated cMB platform containing these plasmids has exhibited significant therapeutic outcomes [136].

Another approach involves DNA-nanoparticles, in which FUS stimulates the microbubbles to release drugs from accompanying nanocarriers. For example, MRgFUS utilizing nano-MBs has been found to enhance the transfection efficiency of the therapeutic *Nrf2* gene [137]. An especially advanced variation utilizes brain-penetrating nanoparticles (BPNs) coated with PEG; when used in conjunction with systemic FUS, these BPNs can lead to dose-related transgene expression. In a rat model of PD, GDNF-BPNs delivered via FUS reached therapeutic levels in the striatum that persisted for up to 10 weeks [138].

The third and particularly effective category, which circumvents the immunogenicity issues linked with viral vectors, involves gene–liposome–MB complexes [122]. Polyethylene glycol (PEG) liposomes are regarded as excellent carriers, and studies employing liposomes encapsulating neurotrophic factor genes (such as BDNF or GDNF) alongside microbubbles and FUS have successfully restored motor function in PD models [124]. These complexes outperform the separate administration of the components because the oscillations of the microbubbles allow the liposomal vector to directly interact with the opened tight-junction pores, enhancing penetration and resulting in more effective gene transfection. Preclinical research has substantiated that delivering BDNF or GDNF genes through this non-viral technique yields a strong neuroprotective effect, preserving dopaminergic neurons and alleviating behavioral deficits [123,124].

Lastly, the fourth category centers on gene-AAV vectors, addressing the prior setbacks in clinical gene therapy that stemmed from invasive procedures and incomplete delivery methods. MRgFUS can non-invasively transport viral vectors like AAV9 and AAV2/1 to designated brain cells [121]. Preclinical investigations have confirmed that FUS-BBB technology combined with a viral vector silencing α-synuclein mitigated the loss of nigrostriatal neurons [120]. This technology has recently progressed to trials in humans and non-human primates, where MRgFUS-mediated BBB opening combined with a systemic AAV vector successfully induced novel protein expression in both the putamen and substantia nigra [122]. Although this offers a promising direction for modulating viral vectors in PD patients, considerable challenges persist, including the high expenses and systemic exposure risks related to the elevated AAV titers required for human trials [135,139]. Future advancements may hinge on the development of neuron-selective AAV serotypes or scalable microbubble drug complexes (MDCs), although issues regarding safety and viral packaging capacity still need addressing [121].

12.3 Safety

Employing MB-FUS to breach the tight junctions among endothelial cells in the BBB and BTB leads to a temporary inflammatory reaction caused by cavitation induced by microbubbles and pulsed thermal injury [140,141]. Safety issues associated with MB-FUS usage involve concerns regarding this inflammatory response and the resulting edema.

12.4 Edema

MB-FUS causes tissue damage in a specific localized area, consisting of three distinct concentric zones: a central hypodense zone exhibiting coagulative necrosis, a sur-

rounding hyperintense zone with cytotoxic edema, and a peripheral area showing weak hyperintensity due to vasogenic edema [142,143]. As mentioned earlier, using larger microbubbles or increasing the intensity of MB-FUS can prolong the permeability of the BBB, but this may lead to the unwanted effect of increased edema. The overall size of the lesion is determined by the total thermal dose applied [141,144]. In a study involving rabbits, cerebral edema was found to develop over 48 hours, with a gradual decrease observed over the next five days [145]. Histological analysis showed central necrosis in the white matter, surrounded by edematous tissue infiltrated with inflammatory cells. In a group of 21 glioblastoma patients who received treatment with an implanted focused ultrasound device for drug delivery, two patients (9.52%) experienced edema that responded positively to steroids and resolved within a few hours [146]. Despite concerns about edema following MB-FUS application, it is generally considered to have a good safety profile. Furthermore, studies have indicated that low-intensity ultrasound stimulation can decrease BBB disruption and alleviate edema in a mouse model of ischemic stroke [147].

13. Inflammation

It is suggested that the pressure on microvessel walls caused by oscillating microbubbles at the focal point of the ultrasound beam, along with the thermal damage from the acoustic pulse, triggers a rapid and brief inflammatory response in the vascular endothelium [125]. This response results in heightened expression of proinflammatory cytokine and chemokine genes, contributing to various effects of MB-FUS, such as neurogenesis, angiogenesis, alterations in transporter expression, increased endocytosis, and decreased immunoreactivity of tight junction proteins. Parameters like ultrasound intensity, pulse repetition frequency, and sonication affect the degree of neuroinflammation, which can clinically present as intracerebral hemorrhage, transient edema, necrosis, and reactive gliosis [126]. The concentration of microbubbles employed does not seem to influence the inflammatory response [148]. During sonication, the microvessels in the brain experience the most significant stress. Nonetheless, different cell types exhibit varied responses to sonication. The activation of vascular endothelial cells triggers the release of proinflammatory cytokines and chemokines, facilitating leukocyte migration across the BBB. The acute activation of astrocytes may offer neuroprotection and aid in preserving stability during sudden ischemic events. Pouliopoulos et al. [149] demonstrated that using MB-FUS to breach the BBB incites a brief immune reaction in the affected area, resulting in an increased microglia density by the second day, which subsided by day 18 without notable clinical deficits in a non-human primate model. They also observed a higher count of immature neurons in regions where the BBB was compromised compared to areas with an intact BBB. Further investigations have identified microstructural alterations even one year following the injury, suggesting significant tissue reorganization [150].

When subjected to physical stress, the vascular endothelium of the CNS produces proinflammatory cytokines and chemokines to safeguard the brain from additional harm. After the thermal injury induced by MB-FUS, there is evidence of pro-inflammatory cytokine gene transcription, which returns to normal after 24 hours [125]. This may elucidate the role of MB-FUS in promoting temporary angiogenic activities and reducing drug outflow. The sterile inflammatory response in the tissue, characterized by the damage-associated molecular pattern (DAMP) response and elevated levels of HSP, IL-1, IL-18, and TNF-α, persists for approximately 24 hours, with macrophages remaining detectable for up to six days after treatment [45]. Chronic inflammation can lead to secondary harm. The pro-inflammatory response subsides and reverts to baseline levels after 24 hours, likely affected by immunoregulatory cytokines from astrocytes and their interactions with microglia. A temporally managed level of inflammation can support the clearance of myelin debris, promote myelin repair, encourage angiogenesis, and assist in the removal of amyloid beta plaques. However, when inflammation remains chronic, it hinders neurogenesis and contributes to apoptosis, necrosis, and various neurodegenerative processes. Researchers have defined safety profiles to optimize the effectiveness of BBB disruption while minimizing chronic inflammation and its adverse effects [151,152].

14. Clinical Studies

Following two decades of promoting preclinical investigations, human trials for FUS combined with microbubbles (MBs) aimed at disrupting the BBB have commenced, with a principal focus on assessing safety [153]. Initial Phase I studies involving patients with conditions like glioblastoma, Alzheimer's disease (AD), and amyotrophic lateral sclerosis have successfully demonstrated the ability to create temporary, localized increases in vascular permeability without causing enduring radiological or neurological issues [154,155,156,157,158]. The first application in humans occurred in 2014 with an implanted ultrasound device (SonoCloud-1) in patients with glioblastoma, which, while requiring surgery, was positively received and suggested potential trends in efficacy [154]. A significant advancement took place in 2015 with the development of the first transcranial FUS system (ExAblate Neuro), which employed phase correction to penetrate the skull and effectively raised chemotherapy concentrations in targeted glioma tissues. Subsequent trials on Alzheimer's patients have further confirmed the safety of undergoing repeated transcranial treatments, even in sensitive areas associated with memory like the hippocampus, without any observed long-term adverse effects up to 15 months after the procedure.

The clinical translation of MR-guided focused ultrasound (MRgFUS) has been progressing rapidly in the last 10 years, and several clinical trials are ongoing and have been completed (both Phase I and Phase II) to determine its safety and feasibility in neurological diseases in neurological diseases, particularly glioblastoma and Alzheimer's disease. Most studies have shown that temporary BBB opening can be safely and reproducibly carried out in a localized manner, with minimal systemic toxicity. The current trials are focusing on optimizing the treatment parameters, evaluation of repeated BBB opening processes, and long-term neurological and cognitive outcomes. Although the clinical translation of FUS-mediated BBB opening has been extensively studied, nanoparticle-assisted FUS drug delivery has not yet been translated to clinical use. Most nanoparticle-based therapeutic systems have shown promising performance in preclinical studies but are still largely under development, due to the challenges of large-scale manufacturing, formulation reproducibility, regulatory approval, and safety. There are ongoing clinical trials that will provide critical evidence of the integration of advanced nanocarriers with image-guided FUS in order to translate precision nanomedicine to central nervous system disorders.

Despite promising preclinical and early clinical outcomes, FUS-assisted nanoparticle-mediated CNS drug delivery remains a complex clinical problem. For large-scale manufacturing, GMP-compliant production, quality assurance, and batch-to-batch reproducibility are needed to ensure the same nanoparticle size, drug loading, surface properties, and biological performance. A variation in the formulation and FUS treatment parameters of nanoparticles may affect the efficacy and safety of the therapy, and therefore the manufacturing and characterization practices should be standardized. Regulatory approval of these platforms is also complicated as they are combination products: a medical device (FUS system), microbubbles, and nanoparticle-based therapeutics. Pharmacokinetics, biodistribution, immunogenicity, long-term safety, and device-drug interactions should be assessed before clinical approval. Furthermore, the clinical implementation is hampered by the need for specialized MRgFUS infrastructure, standardized treatment protocols, trained multidisciplinary teams, and multicenter clinical trials. A solution to these translational barriers is needed for the adoption of FUS-mediated brain drug delivery to be reproducible, safe, and cost-effective.

Despite this strong safety record, there are substantial challenges in applying these findings to clinical settings. A major obstacle is the discrepancy between preclinical models, which typically focus on primary tumor treatment, and the clinical need for post-surgical interventions to address glioma recurrence. Additionally, the significant variability of tumors such as glioblastoma makes them difficult to replicate in animal experiments, leading to preclinical successes that often do not accurately predict human outcomes [64]. As a result, future progress depends on standardizing treatment protocols through a more profound understanding of the complex interactions between ultrasound parameters and microbubble characteristics, as well as developing more predictive models, such as those using human-induced pluripotent stem cells (hiPSCs), to better mimic clinical responses. MRI-guided focused ultrasound (MRgFUS) for transient BBB opening has been translated into clinical practice in the past decade, and a number of Phase I and Phase II clinical trials have been carried out to assess the feasibility and safety of this approach in patients with glioblastoma, Alzheimer's disease, Parkinson's disease, and ALS. All these studies have shown that FUS can deliver localized and reversible BBB opening without major neurological damage if the optimal treatment methods are employed. Early clinical studies have also shown that it is possible to deliver chemotherapeutics and biologics well to brain regions, but there is still no definitive treatment effect in the longer-term randomized studies. In contrast, nanoparticle-assisted brain delivery and FUS are still in the early stage of clinical development. Nanoparticle-based approaches have achieved good results in preclinical studies, and there is only limited clinical evidence in terms of nanoparticle manufacturing, regulatory approval, long-term safety, and standard treatment. We are optimistic that future multicenter clinical trials that combine optimized nanoparticle formulations with MRI-guided FUS will provide important evidence of therapeutic efficacy, safety, and the broader clinical relevance of this approach for CNS disorders.

Recent data regarding clinical studies on the FUS–microbubble–nanoparticle system are given in Table 3 (Ref. [154,155,156,157,158,159,160]).

Nanoparticle-based drug delivery systems in combination with FUS are generally divided into different types with different properties. Polymeric nanoparticles release drugs in a controlled manner and are characterized by strong structural stability and functionalization of surfaces. Liposomes and lipid nanoparticles are biocompatible and encapsulate both hydrophilic and hydrophobic drugs well, leading them to serve as good carriers for nucleic acids and small molecules [58,161]. Polymeric micelles improve the solubility of poorly water-soluble drugs, and dendrimers have very stable and highly branched structures and, thus, are capable of drug loading and a variety of surface modifications. Recently, biomimetic nanocarrier systems such as cell membrane-coated nanoparticles and extracellular vesicle-inspired nanocarriers are promising due to their long circulation, immune protection, and brain targeting ability. Together with transient BBB opening by FUS, these nanocarriers increase the delivery efficiency of the drugs and reduce systemic toxicity. A classification of these nanoparticle systems provides a way of finding appropriate carriers if the therapeutic payload, disease type,

Table 3. Clinical Applications of Focused Ultrasound–Microbubble–Nanoparticle Systems.

Disease/Indication	Clinical trial	NCT number	Phase	Intervention	Status	References
Alzheimer's disease	BBB opening using MRgFUS (ExAblate Neuro)	NCT02986932	Phase I	MRgFUS + Definity® microbubbles	Completed	[155]
Alzheimer's disease	Neuronavigation-guided FUS-induced BBB opening	NCT04118764	Early Phase I	FUS + Definity® microbubbles	Completed	[160]
Alzheimer's disease	Repetitive BBB opening using MRgFUS	NCT06158789	Feasibility	Repeated MRgFUS-mediated BBB opening	Active/Not Recruiting	[154,155,156,157,158]
Glioblastoma	MRgFUS-mediated BBB opening with chemotherapy	NCT02343991	Phase I	MRgFUS + chemotherapy	Completed/ Ongoing	[156]
Parkinson's disease	MRgFUS-guided BBB opening	NCT03608553	Early Phase	MRgFUS	Ongoing	[159]

Table 4. Effect of nanoparticle physicochemical properties on BBB penetration after FUS.

Property	Preferred characteristics	Effect on brain delivery	Design consideration	Ref.
Particle size	20–150 nm	Better BBB penetration and interstitial diffusion	Larger particles show limited penetration	[161]
Surface charge	Neutral/slightly negative	Longer circulation and lower toxicity	Highly positive particles increase nonspecific uptake	[64]
Surface chemistry	PEGylation, ligand functionalization	Reduced protein adsorption and immune clearance	Improves circulation and targeting	[58]
Shape	Mostly spherical; rods/discs under investigation	Influences margination and cellular uptake	Disease-specific optimization required	[58]
Surface ligand density	Optimized receptor affinity	Improves receptor-mediated uptake	Excessive ligand density may reduce circulation	[58]

and pharmacokinetic profile are relevant to the design of next-generation CNS drug delivery strategies [51,100].

Nanoparticle transport across the temporarily disrupted BBB depends on their physicochemical properties such as size, surface charge, surface chemistry, and shape. Nanoparticles with sizes typically ranging from 20 to 150 nm are able to penetrate the temporarily permeabilized BBB, have a long circulation time, and can be removed from the body in a short time. Table 4 (Ref. [58,64,161]) represents data regarding the effect of nanoparticle physicochemical properties on BBB penetration after FUS. The surface charge is also very important, as neutral or slightly negative nanoparticles are more biocompatible (and have a longer circulation time), and highly cationic nanoparticles may increase cellular permeability but at the same time lead to associated toxicity and nonspecific adsorption. The surface chemistry also determines the stability and targeting efficiency of nanoparticles. PEGylation helps in systemic circulation by reducing protein adsorption and macrophage uptake, and ligand-functionalized nanoparticles are able to be taken up by brain endothelial cells and diseased tissues [64]. Moreover, nanoparticle shape affects vascular margination, cellular internalization, and biodistribution, and non-spherical particles have different transport properties compared to spherical ones. These properties and the FUS-mediated BBB opening are key to maximizing drug delivery efficiency, which leads to better outcomes and reduces off-target effects in CNS [130].

Although FUS opening of the BBB allows therapeutic agents to enter the brain, the molecular distribution of such pharmaceutical agents within the brain interstitium is largely regulated by the Extracellular Matrix (ECM), which is another transport barrier [162]. The ECM in the brain is composed of glycosaminoglycans, proteoglycans, hyaluronic acid, and fibrous proteins that form a very dense and negatively charged network that prevents the diffusion and transfer of nanoparticles into the brain. The BBB permeability in the brain interstitium is therefore related to diffusion in the brain and ECM, hydraulic resistance, and interactions between the nanoparticles and ECM [51]. In Table 5 (Ref. [163,164,165,166]) data of optimization of ultrasound parameters for BBB opening were listed. The penetration of nanoparticles in the brain is influenced by the particle size, surface charge, and surface chemistry. Smaller particles with neutral or slightly negative surface charge will generally penetrate the brain more, and the tissue will be more open to the presence of ECM, while diffusion in the brain will be more strongly inhibited if it is large. Current clinical studies of MRgFUS-mediated BBB opening were listed in Table 6 (Ref. [40,156]). The surface modification (PEGylation and biomimetic coatings) also reduces adhesive interactions with the ECM, which improves the interstitial transport and the distribution of therapeutic payloads throughout the target tissue. So, successful CNS drug delivery requires BBB traversal and subsequent tissue penetration to achieve the same therapeutic distribution and to optimize the treatment outcome [130]. Table 7 (Ref. [155,167]) presents major translational challenges for clinical implementation.

15. Future Perspective

Several reviews have discussed focused ultrasound-mediated BBB opening, nanoparticle-based brain drug delivery, or clinical applications of FUS. Most primarily summarize the existing evidence without considering the mechanistic interactions among focused ultrasound, microbubbles, and engineered nanoparticles or critically analyzing the factors influencing their successful clinical translation. Table 8 (Ref. [58,64,100,104,105,106,107,117,118,119,120,121,122,123,124,125,126,127,128,130,131]) represents the therapeutic perspectives of the FUS–microbubble–nanoparticle system. In this review, we focus on the synergistic role of these three components in BBB opening, nanoparticle design, optimization of ultrasound parameters, disease-specific therapeutic applications, nucleic acid delivery, clinical evidence, and translational barriers, among others, such as manufacturing scalability, regulatory concerns, and reproducibility. In Table 9 (Ref. [51,58,64,161]), a comparison of different nanoparticle platforms for FUS-mediated BBB drug delivery is listed. This integrated and critical perspective gives practical insights into the rational

Table 5. Optimization of ultrasound parameters for BBB opening.

Parameter	Typical clinical/ Preclinical range	Influence on BBB opening	Safety considerations	Ref.
Frequency	220–700 kHz	Lower frequency improves skull penetration	Higher frequencies reduce penetration	[163,164]
Acoustic pressure	0.2–0.8 MPa	Determines cavitation intensity	High pressure increases hemorrhage risk	[163,164]
Pulse duration	1–10 ms	Controls BBB permeability	Long pulses increase tissue damage	[163,164]
Pulse repetition frequency	1–10 Hz	Influences cumulative exposure	Requires optimization with pressure	[165,166]
Sonication time	30–120 s	Longer exposure increases delivery	Excessive exposure may induce inflammation	[165,166]
Cavitation monitoring	Passive cavitation detection	Maintains stable cavitation	Prevents inertial cavitation	[165,166]

Table 6. Current clinical studies of MRgFUS-mediated BBB opening.

Disease	Trial stage	Therapeutic strategy	Main findings	Current limitation	Ref.
Glioblastoma	Phase I/ II	MRgFUS + chemotherapy	Safe localized BBB opening; enhanced drug delivery	Small cohorts	[40,156]
Alzheimer's disease	Phase I	MRgFUS	Reversible BBB opening without major adverse events	Long-term efficacy unknown	[40,156]

Table 7. Major translational challenges for clinical implementation.

Challenge	Current limitation	Potential solution	Ref.
Manufacturing scalability	Difficult large-scale GMP production	Automated GMP manufacturing	[155,167]
Batch reproducibility	Variation in particle size and drug loading	Standardized manufacturing protocols	[155,167]
Regulatory approval	Drug-device combination products	Harmonized regulatory framework	[155,167]
Long-term safety	Limited long-term clinical data	Extended follow-up studies	[155,167]
Clinical implementation	MRgFUS infrastructure and expertise required	Multicenter trials and standardized protocols	[155,167]
Cost-effectiveness	High equipment and treatment costs	Technological optimization and commercialization	[155,167]

GMP, good manufacturing practice.

design and future clinical implementation of FUS-assisted nanomedicine for CNS disorders.

In the last almost twenty years, FUS paired with microbubbles [33] has seen remarkable progress, transforming from a conceptual idea to active human clinical trials addressing conditions like Alzheimer's, Parkinson's, and brain tumors. It has become clear that the technique's functions extend beyond simply enhancing drug delivery, as it also induces specific biological responses that could be leveraged for therapeutic use. Nevertheless, most ongoing clinical trials are typically in their initial stages, often limited by small sample sizes and, particularly in neuro-oncology, the challenge of assessing long-term effectiveness due to the poor prognosis associated with glioblastoma. As a result, much of the research tends to focus on short-term safety evaluations instead of definitive efficacy. For this technology to gain wider acceptance for clinical application, the field needs to move toward larger, multicenter, randomized controlled trials to achieve a more comprehensive understanding of the biological effects of the drugs used, fine-tune dosing protocols, and ascertain long-term patient outcomes. Future achievements will also hinge on technological advancements, such as frameless systems and methods that do not depend on costly MRI guidance, to boost cost-effectiveness and accessibility. This will be crucial as investigations broaden into new applications, like using FUS to eliminate amyloid and tau in Alzheimer's disease or enhancing the efficacy of novel immunotherapies like CAR-T cells and other promising chemotherapy agents aimed at brain targets.

Table 8. Therapeutic perspectives of FUS–microbubble–nanoparticle system.

Therapeutic area	Role of FUS–microbubble–nanoparticle system	Therapeutic advantages	Potential outcomes	References
Brain tumors	Enables localized BBB opening for targeted delivery of chemotherapeutic agents and nanomedicines	Improved drug accumulation at tumor site, reduced systemic toxicity, enhanced penetration into tumor tissue	Enhanced antitumor efficacy and prolonged patient survival	[58,64]
Alzheimer's disease	Facilitates delivery of neuroprotective drugs, antibodies, and gene therapeutics across the BBB	Reduction in amyloid-β plaques, improved neuronal targeting, controlled drug release	Improved cognitive function and delayed disease progression	[117,118]
Parkinson's disease	Enhances transport of dopamine-related therapeutics and neurotrophic factors into affected brain regions	Site-specific delivery with minimized peripheral side effects	Restoration of neuronal function and symptom management	[119,120]
Glioblastoma therapy	Assists penetration of nanoparticles carrying anticancer agents into dense tumor microenvironment	Increased therapeutic concentration within glioblastoma tissue	Better tumor suppression and reduced recurrence	[104,105,106,107]
Gene therapy	Supports delivery of plasmids, siRNA, mRNA, and CRISPR-based systems into the CNS	Sustained and controlled genetic expression with targeted cellular uptake	Improved treatment of genetic and neurodegenerative disorders	[120,121,122,123,124]
Epilepsy	Enables focused delivery of antiepileptic drugs to epileptogenic brain regions	Reduced systemic drug exposure and enhanced local therapeutic action	Better seizure control and reduced adverse effects	[127]
Stroke management	Facilitates transport of neuroprotective and regenerative agents to ischemic brain tissue	Enhanced tissue recovery and reduced neuronal damage	Improved neurological recovery and functional outcomes	[128]
CNS infections	Improves brain penetration of antimicrobial agents that poorly cross the BBB	Enhanced localized antimicrobial activity	Effective treatment of resistant or persistent CNS infections	[131]
Neuroinflammation	Allows targeted delivery of anti-inflammatory drugs and biologics	Controlled modulation of inflammatory pathways	Reduction in neuronal damage and inflammation	[125,126]
Precision medicine	Combines imaging-guided BBB modulation with targeted nanocarriers for individualized therapy	Noninvasive, reversible, and patient-specific treatment approach	Safer and more effective personalized brain therapeutics	[58,64,100,130]

Table 9. Comparison of different nanoparticle platforms for FUS-mediated BBB drug delivery.

Nanoparticle platform	Typical composition	Major advantages	Limitations	BBB penetration efficiency	Drug loading capacity	Toxicity profile	Representative applications	References
Polymeric nanoparticles	PLGA, PLA, PEG-PLGA, Chitosan	Controlled release, high stability, surface functionalization	Moderate loading, polymer degradation	Moderate–high	High	Low–moderate	Brain tumors, AD, PD, gene delivery	[161]
Lipid nanoparticles (LNPs)	Ionizable lipids, cholesterol, DSPC	Excellent for RNA delivery, clinically validated	Limited long-term stability	High	Very high	Low	mRNA, siRNA, CRISPR delivery	[64,161]
Liposomes	Phospholipid bilayer	Biocompatible, dual drug encapsulation	Drug leakage, RES uptake	Moderate	High	Low	Glioblastoma, stroke	[51,58,64]
Polymeric micelles	PEG-PCL, PEG-PLA	Solubilize hydrophobic drugs	Limited structural stability	Moderate	Moderate	Low	Brain tumors	[51,58,64]
Dendrimers	PAMAM, PPI	High surface functionality, multivalent targeting	Cationic toxicity	Moderate–high	High	Moderate	Neuroinflammation, glioma	[51,58,64]
Biomimetic nanoparticles	Cell membrane-coated NPs, extracellular vesicles	Immune evasion, prolonged circulation, active targeting	Complex manufacturing	Very high	Moderate	Very low	Brain tumors, neurodegenerative disorders	[51,58,64]

AD, Alzheimer's disease; PD, Parkinson's disease; NPs, nanoparticles; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; RES, reticuloendothelial system.

16. Conclusions

The integrated FUS–microbubble–nanoparticle platform represents the next-generation approach to overcome the BBB and enhance drug delivery to the CNS. It can provide reversible and localized BBB modulation with nanocarriers and also offer improved spatial and therapeutic precision with better targeting of drugs. Future research on ultrasound parameters, microbubble properties, nanoparticle properties, and drug-release properties will be useful to enhance safety and efficacy. Better understanding of the molecular and biological interactions between FUS, microbubbles, nanoparticles, and the brain microenvironment will be essential for the design of rational systems. Long-term efficacy, safety, dosing strategies, and patient outcomes are to be established in large-scale, multicenter, randomized clinical trials. Standardized procedures, reproducible manufacturing, regulatory frameworks, and scalable production will be key for successful clinical translation. Frameless and cost-effective FUS technology will also be a key step to enable wider clinical adoption. This platform could also have therapeutic potential for brain tumors, Alzheimer's and Parkinson's diseases, gene therapy, immunotherapy, and other CNS disorders. In general, further interdisciplinary development will turn FUS-based nanomedicine from an emerging technology to a well-established, precise, and personalized approach to CNS drug delivery.

Author Contributions

PKS and MP contributed to the conceptualization and design of the review, SD contributed to the conception and design of the review and critically reviewed and revised the manuscript, GND contributed to the interpretation and synthesis of the literature. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors acknowledge the scientific contributions of researchers worldwide whose studies have provided valuable insights into focused ultrasound, microbubble technology, and nanoparticle-based brain drug delivery approaches.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Mead BP, Mastorakos P, Suk JS, Klibanov AL, Hanes J, Price RJ. Targeted gene transfer to the brain via the delivery of brain-penetrating DNA nanoparticles with focused ultrasound. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2016; 223: 109–117. https://doi.org/10.1016/j.jconrel.2015.12.034

[2] Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. NeuroRx : the Journal of the American Society for Experimental NeuroTherapeutics. 2005; 2: 3–14. https://doi.org/10.1602/neurorx.2.1.3

[3] Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiology of Disease. 2010; 37: 13–25. https://doi.org/10.1016/j.nbd.2009.07.030

[4] Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008; 57: 178–201. https://doi.org/10.1016/j.neuron.2008.01.003

[5] Daneman R, Prat A. The blood-brain barrier. Cold Spring Harbor Perspectives in Biology. 2015; 7: a020412. https://doi.org/10.1101/cshperspect.a020412

[6] Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. Pharmacological Reviews. 2005; 57: 173–185. https://doi.org/10.1124/pr.57.2.4

[7] Nitta T, Hata M, Gotoh S, Seo Y, Sasaki H, Hashimoto N, et al. Size-selective loosening of the blood-brain barrier in claudin-5-deficient mice. The Journal of Cell Biology. 2003; 161: 653–660. https://doi.org/10.1083/jcb.200302070

[8] Haseloff RF, Dithmer S, Winkler L, Wolburg H, Blasig IE. Transmembrane proteins of the tight junctions at the blood-brain barrier: structural and functional aspects. Seminars in Cell & Developmental Biology. 2015; 38: 16–25. https://doi.org/10.1016/j.semcdb.2014.11.004

[9] Reese TS, Karnovsky MJ. Fine structural localization of a blood-brain barrier to exogenous peroxidase. The Journal of Cell Biology. 1967; 34: 207–217. https://doi.org/10.1083/jcb.34.1.207

[10] Löscher W, Potschka H. Drug resistance in brain diseases and the role of drug efflux transporters. Nature Reviews. Neuroscience. 2005; 6: 591–602. https://doi.org/10.1038/nrn1728

[11] Begley DJ. ABC transporters and the blood-brain barrier. Current Pharmaceutical Design. 2004; 10: 1295–1312. https://doi.org/10.2174/1381612043384844

[12] Miller DS. Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. Trends in Pharmacological Sciences. 2010; 31: 246–254. https://doi.org/10.1016/j.tips.2010.03.003

[13] Mulvihill JJ, Cunnane EM, Ross AM, Duskey JT, Tosi G, Grabrucker AM. Drug delivery across the blood-brain barrier: recent advances in the use of nanocarriers. Nanomedicine (London, England). 2020; 15: 205–214. https://doi.org/10.2217/nnm-2019-0367

[14] Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2016; 235: 34–47. https://doi.org/10.1016/j.jconrel.2016.05.044

[15] Wohlfart S, Gelperina S, Kreuter J. Transport of drugs across the blood-brain barrier by nanoparticles. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2012; 161: 264–273. https://doi.org/10.1016/j.jconrel.2011.08.017

[16] Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics (Oxford, England). 2019; 20: 273–286. https://doi.org/10.1093/biostatistics/kxx069

[17] Vogelbaum MA, Aghi MK. Convection-enhanced delivery for the treatment of glioblastoma. Neuro-Oncology. 2015; 17 Suppl 2: ii3–ii8. https://doi.org/10.1093/neuonc/nou354
[18] Raghavan R, Brady ML, Rodríguez-Ponce MI, Hartlep A, Pedain C, Sampson JH. Convection-enhanced delivery of therapeutics for brain disease, and its optimization. Neurosurgical Focus. 2006; 20: E12. https://doi.org/10.3171/foc.2006.20.4.7
[19] Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR Imaging–guided Focal Opening of the Blood-Brain Barrier in Rabbits. Radiology. 2001; 220: 640–646. https://doi.org/10.1148/radiol.2202001804
[20] McDannold N, Vykhodtseva N, Raymond S, Jolesz FA, Hynynen K. MRI-guided targeted blood-brain barrier disruption with focused ultrasound: histological findings in rabbits. Ultrasound in Medicine & Biology. 2005; 31: 1527–1537. https://doi.org/10.1016/j.ultrasmedbio.2005.07.010
[21] Darrow DP. Focused Ultrasound for Neuromodulation. Neurotherapeutics. 2019; 16: 88–89. https://doi.org/10.1007/s13311-018-00691-3
[22] Marty B, Larrat B, Van Landeghem M, Robic C, Robert P, Port M, et al. Dynamic study of blood-brain barrier closure after its disruption using ultrasound: a quantitative analysis. Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2012; 32: 1948–1958. https://doi.org/10.1038/jcbfm.2012.100
[23] Downs ME, Buch A, Sierra C, Karakatsani ME, Teichert T, Chen S, et al. Long-Term Safety of Repeated Blood-Brain Barrier Opening via Focused Ultrasound with Microbubbles in Non-Human Primates Performing a Cognitive Task. PloS One. 2015; 10: e0125911. https://doi.org/10.1371/journal.pone.0125911
[24] Treat LH, McDannold N, Vykhodtseva N, Zhang Y, Tam K, Hynynen K. Targeted delivery of doxorubicin to the rat brain at therapeutic levels using MRI-guided focused ultrasound. International Journal of Cancer. 2007; 121: 901–907. https://doi.org/10.1002/ijc.22732
[25] Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103: 11719–11723. https://doi.org/10.1073/pnas.0604318103
[26] Jordão JF, Ayala-Grosso CA, Markham K, Huang Y, Chopra R, McLaurin J, et al. Antibodies targeted to the brain with image-guided focused ultrasound reduces amyloid-beta plaque load in the TgCRND8 mouse model of Alzheimer's disease. PloS One. 2010; 5: e10549. https://doi.org/10.1371/journal.pone.0010549
[27] Nance E, Timbie K, Miller GW, Song J, Louttit C, Klibanov AL, et al. Non-invasive delivery of stealth, brain-penetrating nanoparticles across the blood-brain barrier using MRI-guided focused ultrasound. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2014; 189: 123–132. https://doi.org/10.1016/j.jconrel.2014.06.031
[28] Hynynen K. Ultrasound for drug and gene delivery to the brain. Advanced Drug Delivery Reviews. 2008; 60: 1209–1217. https://doi.org/10.1016/j.addr.2008.03.010
[29] Stride E, Saffari N. Microbubble ultrasound contrast agents: a review. Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine. 2003; 217: 429–447. https://doi.org/10.1243/09544110360729072
[30] Sirsi S, Borden M. Microbubble Compositions, Properties and Biomedical Applications. Bubble Science Engineering and Technology. 2009; 1: 3–17. https://doi.org/10.1179/175889709X446507
[31] Ferrara K, Pollard R, Borden M. Ultrasound microbubble contrast agents: fundamentals and application to gene and drug delivery. Annual Review of Biomedical Engineering. 2007; 9: 415–447. https://doi.org/10.1146/annurev.bioeng.8.061505.095852
[32] Faez T, Emmer M, Kooiman K, Versluis M, van der Steen A, de Jong N. 20 years of ultrasound contrast agent modeling. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2013; 60: 7–20. https://doi.org/10.1109/TUFFC.2013.2533
[33] Leighton TG. The Acoustic Bubble. Academic Press: London. 1994.
[34] Apfel RE, Holland CK. Gauging the likelihood of cavitation from short-pulse, low-duty cycle diagnostic ultrasound. Ultrasound in Medicine & Biology. 1991; 17: 179–185. https://doi.org/10.1016/0301-5629(91)90125-g
[35] Tung YS, Vlachos F, Choi JJ, Deffieux T, Selert K, Konofagou EE. In vivo transcranial cavitation threshold detection during ultrasound-induced blood-brain barrier opening in mice. Physics in Medicine and Biology. 2010; 55: 6141–6155. https://doi.org/10.1088/0031-9155/55/20/007
[36] Choi JJ, Wang S, Tung YS, Morrison B, 3rd, Konofagou EE. Molecules of various pharmacologically-relevant sizes can cross the ultrasound-induced blood-brain barrier opening in vivo. Ultrasound in Medicine & Biology. 2010; 36: 58–67. https://doi.org/10.1016/j.ultrasmedbio.2009.08.006
[37] Marmottant P, Hilgenfeldt S. Controlled vesicle deformation and lysis by single oscillating bubbles. Nature. 2003; 423: 153–156. https://doi.org/10.1038/nature01613
[38] Collis J, Manasseh R, Liovic P, Tho P, Ooi A, Petkovic-Duran K, et al. Cavitation microstreaming and stress fields created by microbubbles. Ultrasonics. 2010; 50: 273–279. https://doi.org/10.1016/j.ultras.2009.10.002
[39] Wu J. Theoretical study on shear stress generated by microstreaming surrounding contrast agents attached to living cells. Ultrasound in Medicine & Biology. 2002; 28: 125–129. https://doi.org/10.1016/s0301-5629(01)00497-5
[40] O'Reilly MA, Hynynen K. Blood-brain barrier: real-time feedback-controlled focused ultrasound disruption by using an acoustic emissions-based controller. Radiology. 2012; 263: 96–106. https://doi.org/10.1148/radiol.11111417
[41] McDannold N, Vykhodtseva N, Hynynen K. Targeted disruption of the blood-brain barrier with focused ultrasound: association with cavitation activity. Physics in Medicine and Biology. 2006; 51: 793–807. https://doi.org/10.1088/0031-9155/51/4/003
[42] Flynn HG. Cavitation dynamics. I. A mathematical formulation. The Journal of the Acoustical Society of America. 1975; 57: 1379–1396. https://doi.org/10.1121/1.380624
[43] Postema M, Bouakaz A, Versluis M, de Jong N. Ultrasound-induced gas release from contrast agent microbubbles. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control. 2005; 52: 1035–1041. https://doi.org/10.1109/tuffc.2005.1504026
[44] Coussios CC, Roy RA. Applications of Acoustics and Cavitation to Noninvasive Therapy and Drug Delivery. Annual Review of Fluid Mechanics. 2008; 40: 395–420. https://doi.org/10.1146/annurev.fluid.40.111406.102116
[45] Kovacs ZI, Kim S, Jikaria N, Qureshi F, Milo B, Lewis BK, et al. Disrupting the blood-brain barrier by focused ultrasound induces sterile inflammation. Proceedings of the National Academy of Sciences of the United States of America. 2017; 114: E75–E84. https://doi.org/10.1073/pnas.1614777114
[46] Chen S, Nazeri A, Baek H, Ye D, Yang Y, Yuan J, et al. A review of bioeffects induced by focused ultrasound combined with microbubbles on the neurovascular unit. Journal of Cerebral Blood Flow and Metabolism. 2022; 42: 3–26. https://doi.org/10.1177/0271678X211046129
[47] Pagé G, Novell A, Larrat B. Imaging strategies to assess efficacy and safety of ultrasound-induced blood-brain barrier opening. npj Acoustics. 2025; 1: 20.

[48] Kooiman K, Vos HJ, Versluis M, de Jong N. Acoustic behavior of microbubbles and implications for drug delivery. Advanced Drug Delivery Reviews. 2014; 72: 28–48. https://doi.org/10.1016/j.addr.2014.03.003

[49] Deng J, Huang Q, Wang F, Liu Y, Wang Z, Wang Z, et al. The role of caveolin-1 in blood-brain barrier disruption induced by focused ultrasound combined with microbubbles. Journal of Molecular Neuroscience : MN. 2012; 46: 677–687. https://doi.org/10.1007/s12031-011-9629-9

[50] Sheikov N, McDannold N, Vykhodtseva N, Jolesz F, Hynynen K. Cellular mechanisms of the blood-brain barrier opening induced by ultrasound in presence of microbubbles. Ultrasound in Medicine & Biology. 2004; 30: 979–989. https://doi.org/10.1016/j.ultrasmedbio.2004.04.010

[51] Ding L, Kshirsagar P, Agrawal P, Murry DJ. Crossing the Blood-Brain Barrier: Innovations in Receptor- and Transporter-Mediated Transcytosis Strategies. Pharmaceutics. 2025; 17: 706. https://doi.org/10.3390/pharmaceutics17060706

[52] Zamat A. Tumor-Localized Control of CAR T Cells to Potentiate Solid Tumor Immunotherapy [Doctoral dissertation]. Georgia Institute of Technology. 2024.

[53] Chai WY, Chu PC, Tsai MY, Lin YC, Wang JJ, Wei KC, et al. Magnetic-resonance imaging for kinetic analysis of permeability changes during focused ultrasound-induced blood-brain barrier opening and brain drug delivery. Journal of Controlled Release. 2014; 192: 1–9. https://doi.org/10.1016/j.jconrel.2014.06.023

[54] Treat LH, McDannold N, Zhang Y, Vykhodtseva N, Hynynen K. Improved anti-tumor effect of liposomal doxorubicin after targeted blood-brain barrier disruption by MRI-guided focused ultrasound in rat glioma. Ultrasound in Medicine & Biology. 2012; 38: 1716–1725. https://doi.org/10.1016/j.ultrasmedbio.2012.04.015

[55] McDannold N, Vykhodtseva N, Hynynen K. Effects of Acoustic Parameters and Ultrasound Contrast Agent Dose on Focused-Ultrasound Induced Blood-Brain Barrier Disruption. Ultrasound in Medicine & Biology. 2008; 34: 930–937. https://doi.org/10.1016/j.ultrasmedbio.2007.11.009

[56] Burgess A, Shah K, Hough O, Hynynen K. Focused ultrasound-mediated drug delivery through the blood-brain barrier. Expert Review of Neurotherapeutics. 2015; 15: 477–491. https://doi.org/10.1586/14737175.2015.1028369

[57] Dasgupta A, Liu M, Ojha T, Storm G, Kiessling F, Lammers T. Ultrasound-mediated drug delivery to the brain: principles, progress and prospects. Drug Discovery Today. Technologies. 2016; 20: 41–48. https://doi.org/10.1016/j.ddtec.2016.07.007

[58] Zhang S, Zhang S, Luo S, Tang P, Wan M, Wu D, et al. Ultrasound-assisted brain delivery of nanomedicines for brain tumor therapy: advance and prospect. Journal of Nanobiotechnology. 2022; 20: 287. https://doi.org/10.1186/s12951-022-01464-z

[59] Barzegar-Fallah A, Gandhi K, Rizwan SB, Slatter TL, Reynolds JNJ. Harnessing Ultrasound for Targeting Drug Delivery to the Brain and Breaching the Blood-Brain Tumour Barrier. Pharmaceutics. 2022; 14: 2231. https://doi.org/10.3390/pharmaceutics14102231

[60] Martinez P, Nault G, Steiner J, Wempe MF, Pierce A, Brunt B, et al. MRI-guided focused ultrasound blood-brain barrier opening increases drug delivery and efficacy in a diffuse midline glioma mouse model. Neuro-oncology Advances. 2023; 5: vdad111. https://doi.org/10.1093/noajnl/vdad111

[61] Phillips LC, Dhanaliwala AH, Klibanov AL, Hossack JA, Wamhoff BR. Focused ultrasound-mediated drug delivery from microbubbles reduces drug dose necessary for therapeutic effect on neointima formation--brief report. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011; 31: 2853–2855. https://doi.org/10.1161/ATVBAHA.111.238170

[62] Wu SY, Sanchez CS, Samiotaki G, Buch A, Ferrera VP, Konofagou EE. Characterizing Focused-Ultrasound Mediated Drug Delivery to the Heterogeneous Primate Brain In Vivo with Acoustic Monitoring. Scientific Reports. 2016; 6: 37094. https://doi.org/10.1038/srep37094

[63] Arsiwala TA, Sprowls SA, Blethen KE, Adkins CE, Saralkar PA, Fladeland RA, et al. Ultrasound-mediated disruption of the blood tumor barrier for improved therapeutic delivery. Neoplasia (New York, N.Y.). 2021; 23: 676–691. https://doi.org/10.1016/j.neo.2021.04.005

[64] Brighi C, Salimova E, de Veer M, Puttick S, Egan G. Translation of focused ultrasound for blood-brain barrier opening in glioma. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2022; 345: 443–463. https://doi.org/10.1016/j.jconrel.2022.03.035

[65] Wang S, Chen Y, Guo J, Huang Q. Liposomes for Tumor Targeted Therapy: A Review. International Journal of Molecular Sciences. 2023; 24: 2643. https://doi.org/10.3390/ijms24032643

[66] Tenchov R, Bird R, Curtze AE, Zhou Q. Lipid Nanoparticles─From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. ACS Nano. 2021; 15: 16982–17015. https://doi.org/10.1021/acsnano.1c04996

[67] Kim YS, Ko MJ, Moon H, Sim W, Cho AS, Gil G, et al. Ultrasound-Responsive Liposomes for Targeted Drug Delivery Combined with Focused Ultrasound. Pharmaceutics. 2022; 14: 1314. https://doi.org/10.3390/pharmaceutics14071314

[68] Papachristodoulou A, Signorell RD, Werner B, Brambilla D, Luciani P, Cavusoglu M, et al. Chemotherapy sensitization of glioblastoma by focused ultrasound-mediated delivery of therapeutic liposomes. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2019; 295: 130–139. https://doi.org/10.1016/j.jconrel.2018.12.009

[69] Zhang X, Hu J, Zhao G, Huang N, Tan Y, Pi L, et al. PEGylated PLGA-based phase shift nanodroplets combined with focused ultrasound for blood brain barrier opening in rats. Oncotarget. 2017; 8: 38927–38936. https://doi.org/10.18632/oncotarget.17155

[70] Wang F, Dong L, Liang S, Wei X, Wang Y, Chang L, et al. Ultrasound-triggered drug delivery for glioma therapy through gambogic acid-loaded nanobubble-microbubble complexes. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2022; 150: 113042. https://doi.org/10.1016/j.biopha.2022.113042

[71] Hersh AM, Bhimreddy M, Weber-Levine C, Jiang K, Alomari S, Theodore N, et al. Applications of Focused Ultrasound for the Treatment of Glioblastoma: A New Frontier. Cancers. 2022; 14: 4920. https://doi.org/10.3390/cancers14194920

[72] Mody VV, Cox A, Shah S, Singh A, Bevins W, Parihar H. Magnetic nanoparticle drug delivery systems for targeting tumor. Applied Nanoscience. 2014; 4: 385–392. https://doi.org/10.1007/s13204-013-0216-y

[73] Yang HW, Hua MY, Liu HL, Huang CY, Wei KC. Potential of magnetic nanoparticles for targeted drug delivery. Nanotechnology, Science and Applications. 2012; 5: 73–86. https://doi.org/10.2147/NSA.S35506

[74] Huang J, Li Y, Orza A, Lu Q, Guo P, Wang L, et al. Magnetic Nanoparticle Facilitated Drug Delivery for Cancer Therapy with Targeted and Image-Guided Approaches. Advanced Functional Materials. 2016; 26: 3818–3836. https://doi.org/10.1002/adfm.201504185

[75] Spoială A, Ilie CI, Motelica L, Ficai D, Semenescu A, Oprea OC, et al. Smart Magnetic Drug Delivery Systems for the Treatment of Cancer. Nanomaterials (Basel, Switzerland). 2023; 13: 876. https://doi.org/10.3390/nano13050876

[76] Zeng S, Tang Q, Xiao M, Tong X, Yang T, Yin D, et al. Cell

membrane-coated nanomaterials for cancer therapy. Materials Today. Bio. 2023; 20: 100633. https://doi.org/10.1016/j.mtbio.2023.100633

[77] Wahajuddin, Arora S. Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. International Journal of Nanomedicine. 2012; 7: 3445–3471. https://doi.org/10.2147/IJN.S30320

[78] Marino A, Camponovo A, Degl'Innocenti A, Bartolucci M, Tapeinos C, Martinelli C, et al. Multifunctional temozolomide-loaded lipid superparamagnetic nanovectors: dual targeting and disintegration of glioblastoma spheroids by synergic chemotherapy and hyperthermia treatment. Nanoscale. 2019; 11: 21227–21248. https://doi.org/10.1039/c9nr07976a

[79] Włodarczyk A, Gorgoń S, Radoń A, Bajdak-Rusinek K. Magnetite Nanoparticles in Magnetic Hyperthermia and Cancer Therapies: Challenges and Perspectives. Nanomaterials (Basel, Switzerland). 2022; 12: 1807. https://doi.org/10.3390/nano12111807

[80] Chang D, Lim M, Goos JACM, Qiao R, Ng YY, Mansfeld FM, et al. Biologically Targeted Magnetic Hyperthermia: Potential and Limitations. Frontiers in Pharmacology. 2018; 9: 831. https://doi.org/10.3389/fphar.2018.00831

[81] Michael JS, Lee BS, Zhang M, Yu JS. Nanotechnology for Treatment of Glioblastoma Multiforme. Journal of Translational Internal Medicine. 2018; 6: 128–133. https://doi.org/10.2478/jtim-2018-0025

[82] Wankhede M, Bouras A, Kaluzova M, Hadjipanayis CG. Magnetic nanoparticles: an emerging technology for malignant brain tumor imaging and therapy. Expert Review of Clinical Pharmacology. 2012; 5: 173–186. https://doi.org/10.1586/ecp.12.1

[83] Kim KR, Lee AS, Kim SM, Heo HR, Kim CS. Virus-like nanoparticles as a theranostic platform for cancer. Frontiers in Bioengineering and Biotechnology. 2023; 10: 1106767. https://doi.org/10.3389/fbioe.2022.1106767

[84] Mohsen MO, Bachmann MF. Virus-like particle vaccinology, from bench to bedside. Cellular & Molecular Immunology. 2022; 19: 993–1011. https://doi.org/10.1038/s41423-022-00897-8

[85] Kim KS. Investigating Bacterial Penetration of the Blood-Brain Barrier for the Pathogenesis, Prevention, and Therapy of Bacterial Meningitis. ACS Infectious Diseases. 2020; 6: 34–42. https://doi.org/10.1021/acsinfecdis.9b00319

[86] Ye D, Zimmermann T, Demina V, Sotnikov S, Ried CL, Rahn H, et al. Trafficking of JC virus-like particles across the blood-brain barrier. Nanoscale Advances. 2021; 3: 2488–2500. https://doi.org/10.1039/d0na00879f

[87] Nowak I, Madej M, Secemska J, Sarna R, Strzalka-Mrozik B. Virus-Based Biological Systems as Next-Generation Carriers for the Therapy of Central Nervous System Diseases. Pharmaceutics. 2023; 15: 1931. https://doi.org/10.3390/pharmaceutics15071931

[88] Chen YL, Bao CJ, Duan JL, Xie Y, Lu WL. Overcoming biological barriers by virus-like drug particles for drug delivery. Advanced Drug Delivery Reviews. 2023; 203: 115134. https://doi.org/10.1016/j.addr.2023.115134

[89] Henkin RI. Intranasal delivery to the brain. Nature Biotechnology. 2011; 29: 480. https://doi.org/10.1038/nbt.1866

[90] Hanson LR, Frey WH, 2nd. Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease. BMC Neuroscience. 2008; 9 Suppl 3: S5. https://doi.org/10.1186/1471-2202-9-S3-S5

[91] Jeong SH, Jang JH, Lee YB. Drug delivery to the brain via the nasal route of administration: exploration of key targets and major consideration factors. Journal of Pharmaceutical Investigation. 2023; 53: 119–152. https://doi.org/10.1007/s40005-022-00589-5

[92] Formica ML, Real DA, Picchio ML, Catlin E, Donnelly RF, Paredes AJ. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. Applied Materials Today. 2022; 29: 101631. https://doi.org/10.1016/j.apmt.2022.101631

[93] Lee D, Minko T. Nanotherapeutics for Nose-to-Brain Drug Delivery: An Approach to Bypass the Blood Brain Barrier. Pharmaceutics. 2021; 13: 2049. https://doi.org/10.3390/pharmaceutics13122049

[94] Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sciences. 2018; 195: 44–52. https://doi.org/10.1016/j.lfs.2017.12.025

[95] Nooraei S, Bahrulolum H, Hoseini ZS, Katalani C, Hajizade A, Easton AJ, et al. Virus-like particles: preparation, immunogenicity and their roles as nanovaccines and drug nanocarriers. Journal of Nanobiotechnology. 2021; 19: 59. https://doi.org/10.1186/s12951-021-00806-7

[96] Ikwuagwu B, Tullman-Ercek D. Virus-like particles for drug delivery: a review of methods and applications. Current Opinion in Biotechnology. 2022; 78: 102785. https://doi.org/10.1016/j.copbio.2022.102785

[97] Baghirov H, Snipstad S, Sulheim E, Berg S, Hansen R, Thorsen F, et al. Ultrasound-mediated delivery and distribution of polymeric nanoparticles in the normal brain parenchyma of a metastatic brain tumour model. PloS One. 2018; 13: e0191102. https://doi.org/10.1371/journal.pone.0191102

[98] Ogawa K, Kato N, Yoshida M, Hiu T, Matsuo T, Mizukami S, et al. Focused ultrasound/microbubbles-assisted BBB opening enhances LNP-mediated mRNA delivery to brain. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2022; 348: 34–41. https://doi.org/10.1016/j.jconrel.2022.05.042

[99] Shumer-Elbaz M, Ad-El N, Chulanova Y, Brier D, Goldsmith M, Bismuth M, et al. Low-frequency ultrasound-mediated blood-brain barrier opening enables non-invasive lipid nanoparticle RNA delivery to glioblastoma. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 385: 114018. https://doi.org/10.1016/j.jconrel.2025.114018

[100] Liu S, Jin X, Ge Y, Dong J, Liu X, Pei X, et al. Advances in brain-targeted delivery strategies and natural product-mediated enhancement of blood-brain barrier permeability. Journal of Nanobiotechnology. 2025; 23: 382. https://doi.org/10.1186/s12951-025-03415-w

[101] Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015-2019. Neuro-Oncology. 2022; 24: v1–v95. https://doi.org/10.1093/neuonc/noac202

[102] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncology. 2021; 23: 1231–1251. https://doi.org/10.1093/neuonc/noab106

[103] Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nature Reviews. Cancer. 2020; 20: 26–41. https://doi.org/10.1038/s41568-019-0205-x

[104] Dong Q, He L, Chen L, Deng Q. Opening the Blood-Brain Barrier and Improving the Efficacy of Temozolomide Treatments of Glioblastoma Using Pulsed, Focused Ultrasound with a Microbubble Contrast Agent. BioMed Research International. 2018; 2018: 6501508. https://doi.org/10.1155/2018/6501508

[105] Liu HL, Huang CY, Chen JY, Wang HYJ, Chen PY, Wei KC. Pharmacodynamic and therapeutic investigation of focused ultrasound-induced blood-brain barrier opening for enhanced

temozolomide delivery in glioma treatment. PloS One. 2014; 9: e114311. https://doi.org/10.1371/journal.pone.0114311
[106] Wei KC, Chu PC, Wang HYJ, Huang CY, Chen PY, Tsai HC, et al. Focused ultrasound-induced blood-brain barrier opening to enhance temozolomide delivery for glioblastoma treatment: a preclinical study. PloS One. 2013; 8: e58995. https://doi.org/10.1371/journal.pone.0058995
[107] Dréan A, Lemaire N, Bouchoux G, Goldwirt L, Canney M, Goli L, et al. Temporary blood-brain barrier disruption by low intensity pulsed ultrasound increases carboplatin delivery and efficacy in preclinical models of glioblastoma. Journal of Neuro-oncology. 2019; 144: 33–41. https://doi.org/10.1007/s11060-019-03204-0
[108] Pacia CP, Zhu L, Yang Y, Yue Y, Nazeri A, Michael Gach H, et al. Feasibility and safety of focused ultrasound-enabled liquid biopsy in the brain of a porcine model. Scientific Reports. 2020; 10: 7449. https://doi.org/10.1038/s41598-020-64440-3
[109] Zhu L, Cheng G, Ye D, Nazeri A, Yue Y, Liu W, et al. Focused Ultrasound-enabled Brain Tumor Liquid Biopsy. Scientific Reports. 2018; 8: 6553. https://doi.org/10.1038/s41598-018-24516-7
[110] Yuan J, Xu L, Chien CY, Yang Y, Yue Y, Fadera S, et al. First-in-human prospective trial of sonobiopsy in high-grade glioma patients using neuronavigation-guided focused ultrasound. NPJ Precision Oncology. 2023; 7: 92. https://doi.org/10.1038/s41698-023-00448-y
[111] McMahon D, Hynynen K. Acute Inflammatory Response Following Increased Blood-Brain Barrier Permeability Induced by Focused Ultrasound is Dependent on Microbubble Dose. Theranostics. 2017; 7: 3989–4000. https://doi.org/10.7150/thno.21630
[112] Sheybani ND, Witter AR, Garrison WJ, Miller GW, Price RJ, Bullock TNJ. Profiling of the immune landscape in murine glioblastoma following blood brain/tumor barrier disruption with MR image-guided focused ultrasound. Journal of Neuro-oncology. 2022; 156: 109–122. https://doi.org/10.1007/s11060-021-03887-4
[113] Sabbagh A, Beccaria K, Ling X, Marisetty A, Ott M, Caruso H, et al. Opening of the Blood-Brain Barrier Using Low-Intensity Pulsed Ultrasound Enhances Responses to Immunotherapy in Preclinical Glioma Models. Clinical Cancer Research : an Official Journal of the American Association for Cancer Research. 2021; 27: 4325–4337. https://doi.org/10.1158/1078-0432.CCR-20-3760
[114] Bonosi L, Marino S, Benigno UE, Musso S, Buscemi F, Giardina K, et al. Sonodynamic therapy and magnetic resonance-guided focused ultrasound: new therapeutic strategy in glioblastoma. Journal of Neuro-oncology. 2023; 163: 219–238. https://doi.org/10.1007/s11060-023-04333-3
[115] Wu SK, Santos MA, Marcus SL, Hynynen K. MR-guided Focused Ultrasound Facilitates Sonodynamic Therapy with 5-Aminolevulinic Acid in a Rat Glioma Model. Scientific Reports. 2019; 9: 10465. https://doi.org/10.1038/s41598-019-46832-2
[116] Zhou Y, Jiao J, Yang R, Wen B, Wu Q, Xu L, et al. Temozolomide-based sonodynamic therapy induces immunogenic cell death in glioma. Clinical Immunology (Orlando, Fla.). 2023; 256: 109772. https://doi.org/10.1016/j.clim.2023.109772
[117] Burgess A, Dubey S, Yeung S, Hough O, Eterman N, Aubert I, et al. Alzheimer Disease in a Mouse Model: MR Imaging–guided Focused Ultrasound Targeted to the Hippocampus Opens the Blood-Brain Barrier and Improves Pathologic Abnormalities and Behavior. Radiology. 2014; 273: 736–745. https://doi.org/10.1148/radiol.14140245
[118] Leinenga G, Götz J. Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer's disease mouse model. Science Translational Medicine. 2015; 7: 278ra33. https://doi.org/10.1126/scitranslmed.aaa2512
[119] Baseri B, Choi JJ, Deffieux T, Samiotaki G, Tung YS, Olumolade O, et al. Activation of signaling pathways following localized delivery of systemically administered neurotrophic factors across the blood-brain barrier using focused ultrasound and microbubbles. Physics in Medicine and Biology. 2012; 57: N65–N81. https://doi.org/10.1088/0031-9155/57/7/N65
[120] Xhima K, Nabbouh F, Hynynen K, Aubert I, Tandon A. Noninvasive delivery of an α-synuclein gene silencing vector with magnetic resonance-guided focused ultrasound. Movement Disorders : Official Journal of the Movement Disorder Society. 2018; 33: 1567–1579. https://doi.org/10.1002/mds.101
[121] Noroozian Z, Xhima K, Huang Y, Kaspar BK, Kügler S, Hynynen K, et al. MRI-Guided Focused Ultrasound for Targeted Delivery of rAAV to the Brain. Methods in Molecular Biology (Clifton, N.J.). 2019; 1950: 177–197. https://doi.org/10.1007/978-1-4939-9139-6_10
[122] Lin CY, Hsieh HY, Pitt WG, Huang CY, Tseng IC, Yeh CK, et al. Focused ultrasound-induced blood-brain barrier opening for non-viral, non-invasive, and targeted gene delivery. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2015; 212: 1–9. https://doi.org/10.1016/j.jconrel.2015.06.010
[123] Lin CY, Hsieh HY, Chen CM, Wu SR, Tsai CH, Huang CY, et al. Non-invasive, neuron-specific gene therapy by focused ultrasound-induced blood-brain barrier opening in Parkinson's disease mouse model. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2016; 235: 72–81. https://doi.org/10.1016/j.jconrel.2016.05.052
[124] Lin CY, Lin YC, Huang CY, Wu SR, Chen CM, Liu HL. Ultrasound-responsive neurotrophic factor-loaded microbubble-liposome complex: Preclinical investigation for Parkinson's disease treatment. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2020; 321: 519–528. https://doi.org/10.1016/j.jconrel.2020.02.044
[125] McMahon D, Bendayan R, Hynynen K. Acute effects of focused ultrasound-induced increases in blood-brain barrier permeability on rat microvascular transcriptome. Scientific Reports. 2017; 7: 45657. https://doi.org/10.1038/srep45657
[126] Choi HJ, Han M, Seo H, Park CY, Lee EH, Park J. The new insight into the inflammatory response following focused ultrasound-mediated blood–brain barrier disruption. Fluids and Barriers of the CNS. 2022; 19: 103. https://doi.org/10.1186/s12987-022-00402-3
[127] Succop BS Jr, Seas A, Woo J, Bode Padron KJ, Bartlett AM, Shah B, et al. Focused Ultrasound in the Treatment of Epilepsy: Current Applications and Future Directions. Stereotactic and Functional Neurosurgery. 2025; 103: 166–188. https://doi.org/10.1159/000545716
[128] Dong W, Wang G, Chai Y, Li W, Liu S, Liu H, et al. Two-step ultrasonic cavitation controlled delivery of brain exogenous nucleic acids for ischemic stroke using acoustic-cationic-polymeric-nanodroplets. Drug Delivery and Translational Research. 2025; 15: 3695–3715. https://doi.org/10.1007/s13346-025-01828-6
[129] Raymond SB, Treat LH, Dewey JD, McDannold NJ, Hynynen K, Bacskai BJ. Ultrasound Enhanced Delivery of Molecular Imaging and Therapeutic Agents in Alzheimer's Disease Mouse Models. PLoS ONE. 2008; 3: e2175. https://doi.org/10.1371/journal.pone.0002175
[130] Baek H, Lockwood D, Mason EJ, Obusez E, Poturalski M, Rammo R, et al. Clinical Intervention Using Focused Ultrasound (FUS) Stimulation of the Brain in Diverse Neurological Disorders. Frontiers in Neurology. 2022; 13: 880814. https://doi.org/10.3389/fneur.2022.880814
[131] Lanser DM, Turner A, Pacifici N, Vu K, Lewis J, Gelli A. Con-

jugation of a Cryptococcus neoformans-derived metalloprotease to antifungal-loaded PLGA nanoparticles treats neural cryptococcosis in an in vitro model. PloS One. 2026; 21: e0340202. https://doi.org/10.1371/journal.pone.0340202

[132] Nisbet RM, Van der Jeugd A, Leinenga G, Evans HT, Janowicz PW, Götz J. Combined effects of scanning ultrasound and a tau-specific single chain antibody in a tau transgenic mouse model. Brain. 2017; 140: 1220–1230. https://doi.org/10.1093/brain/awx052

[133] Hsu PH, Lin YT, Chung YH, Lin KJ, Yang LY, Yen TC, et al. Focused Ultrasound-Induced Blood-Brain Barrier Opening Enhances GSK-3 Inhibitor Delivery for Amyloid-Beta Plaque Reduction. Scientific Reports. 2018; 8: 12882. https://doi.org/10.1038/s41598-018-31071-8

[134] Dubey S, Heinen S, Krantic S, McLaurin J, Branch DR, Hynynen K, et al. Clinically approved IVIg delivered to the hippocampus with focused ultrasound promotes neurogenesis in a model of Alzheimer's disease. Proceedings of the National Academy of Sciences. 2020; 117: 32691–32700. https://doi.org/10.1073/pnas.1908658117

[135] Karakatsani ME, Blesa J, Konofagou EE. Blood-brain barrier opening with focused ultrasound in experimental models of Parkinson's disease. Movement Disorders : Official Journal of the Movement Disorder Society. 2019; 34: 1252–1261. https://doi.org/10.1002/mds.27804

[136] Fan CH, Ting CY, Lin CY, Chan HL, Chang YC, Chen YY, et al. Noninvasive, Targeted, and Non-Viral Ultrasound-Mediated GDNF-Plasmid Delivery for Treatment of Parkinson's Disease. Scientific Reports. 2016; 6: 19579. https://doi.org/10.1038/srep19579

[137] Long L, Cai X, Guo R, Wang P, Wu L, Yin T, et al. Treatment of Parkinson's disease in rats by Nrf2 transfection using MRI-guided focused ultrasound delivery of nanomicrobubbles. Biochemical and Biophysical Research Communications. 2017; 482: 75–80. https://doi.org/10.1016/j.bbrc.2016.10.141

[138] Karakatsani ME, Wang S, Samiotaki G, Kugelman T, Olumolade OO, Acosta C, et al. Amelioration of the nigrostriatal pathway facilitated by ultrasound-mediated neurotrophic delivery in early Parkinson's disease. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2019; 303: 289–301. https://doi.org/10.1016/j.jconrel.2019.03.030

[139] Meng Y, Voisin MR, Suppiah S, Kalia SK, Kalia LV, Hamani C, et al. Is there a role for MR-guided focused ultrasound in Parkinson's disease? Movement Disorders : Official Journal of the Movement Disorder Society. 2018; 33: 575–579. https://doi.org/10.1002/mds.27308

[140] Ji R, Karakatsani ME, Burgess M, Smith M, Murillo MF, Konofagou EE. Cavitation-modulated inflammatory response following focused ultrasound blood-brain barrier opening. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2021; 337: 458–471. https://doi.org/10.1016/j.jconrel.2021.07.042

[141] Jones RM, Kamps S, Huang Y, Scantlebury N, Lipsman N, Schwartz ML, et al. Accumulated thermal dose in MRI-guided focused ultrasound for essential tremor: repeated sonications with low focal temperatures. Journal of Neurosurgery. 2019; 132: 1802–1809. https://doi.org/10.3171/2019.2.jns182995

[142] Harary M, Essayed WI, Valdes PA, McDannold N, Cosgrove GR. Volumetric analysis of magnetic resonance-guided focused ultrasound thalamotomy lesions. Neurosurgical Focus. 2018; 44: E6. https://doi.org/10.3171/2017.11.FOCUS17587

[143] Wintermark M, Druzgal J, Huss DS, Khaled MA, Monteith S, Raghavan P, et al. Imaging Findings in MR Imaging-Guided Focused Ultrasound Treatment for Patients with Essential Tremor. AJNR. American Journal of Neuroradiology. 2014; 35: 891–896. https://doi.org/10.3174/ajnr.a3808

[144] Huang Y, Lipsman N, Schwartz ML, Krishna V, Sammartino F, Lozano AM, et al. Predicting lesion size by accumulated thermal dose in MR-guided focused ultrasound for essential tremor. Medical Physics. 2018; 45: 4704–4710. https://doi.org/10.1002/mp.13126

[145] Allen SP, Prada F, Xu Z, Gatesman J, Feng X, Sporkin H, et al. A preclinical study of diffusion-weighted MRI contrast as an early indicator of thermal ablation. Magnetic Resonance in Medicine. 2021; 85: 2145–2159. https://doi.org/10.1002/mrm.28537

[146] Idbaih A, Canney M, Belin L, Desseaux C, Vignot A, Bouchoux G, et al. Safety and Feasibility of Repeated and Transient Blood–Brain Barrier Disruption by Pulsed Ultrasound in Patients with Recurrent Glioblastoma. Clinical Cancer Research. 2019; 25: 3793–3801. https://doi.org/10.1158/1078-0432.ccr-18-3643

[147] Yang GY, Wang JX, Deng LD, Qi L, Suo Q, Wu SJ, et al. Transcranial focused ultrasound stimulation reduces vasogenic edema after middle cerebral artery occlusion in mice. Neural Regeneration Research. 2022; 17: 2058–2063. https://doi.org/10.4103/1673-5374.335158

[148] Pascal A, Li N, Lechtenberg KJ, Rosenberg J, Airan RD, James ML, et al. Histologic evaluation of activation of acute inflammatory response in a mouse model following ultrasound-mediated blood-brain barrier using different acoustic pressures and microbubble doses. Nanotheranostics. 2020; 4: 210–223. https://doi.org/10.7150/ntno.49898

[149] Pouliopoulos AN, Kwon N, Jensen G, Meaney A, Niimi Y, Burgess MT, et al. Safety evaluation of a clinical focused ultrasound system for neuronavigation guided blood-brain barrier opening in non-human primates. Scientific Reports. 2021; 11: 15043. https://doi.org/10.1038/s41598-021-94188-3

[150] Sammartino F, Yeh FC, Krishna V. Longitudinal analysis of structural changes following unilateral focused ultrasound thalamotomy. NeuroImage. Clinical. 2019; 22: 101754. https://doi.org/10.1016/j.nicl.2019.101754

[151] Shin J, Kong C, Cho JS, Lee J, Koh CS, Yoon MS, et al. Focused ultrasound–mediated noninvasive blood-brain barrier modulation: preclinical examination of efficacy and safety in various sonication parameters. Neurosurgical Focus. 2018; 44: E15. https://doi.org/10.3171/2017.11.focus17627

[152] O'Reilly MA, Jones RM, Barrett E, Schwab A, Head E, Hynynen K. Investigation of the Safety of Focused Ultrasound-Induced Blood-Brain Barrier Opening in a Natural Canine Model of Aging. Theranostics. 2017; 7: 3573–3584. https://doi.org/10.7150/thno.20621

[153] Mörocz IÁ, Hynynen K, Gudbjartsson H, Peled S, Colucci V, Jólesz FA. Invited. Brain edema development after MRI-guided focused ultrasound treatment. Journal of Magnetic Resonance Imaging. 1998; 8: 136–142. https://doi.org/10.1002/jmri.1880080126

[154] Carpentier A, Canney M, Vignot A, Reina V, Beccaria K, Horodyckid C, et al. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. Science Translational Medicine. 2016; 8: 343re2. https://doi.org/10.1126/scitranslmed.aaf6086

[155] Lipsman N, Meng Y, Bethune AJ, Huang Y, Lam B, Masellis M, et al. Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nature Communications. 2018; 9: 2336. https://doi.org/10.1038/s41467-018-04529-6

[156] Mainprize T, Lipsman N, Huang Y, Meng Y, Bethune A, Ironside S, et al. Blood-Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study. Scientific Reports. 2019; 9: 321. https://doi.org/10.1038/s41598-018-36340-0

[157] Rezai AR, Ranjan M, D'Haese PF, Haut MW, Carpenter J, Najib U, et al. Noninvasive hippocampal blood-brain barrier open-

ing in Alzheimer's disease with focused ultrasound. Proceedings of the National Academy of Sciences of the United States of America. 2020; 117: 9180–9182. https://doi.org/10.1073/pnas.2002571117

[158] Abrahao A, Meng Y, Llinas M, Huang Y, Hamani C, Mainprize T, et al. First-in-human trial of blood–brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. Nature Communications. 2019; 10: 4373. https://doi.org/10.1038/s41467-019-12426-9

[159] Gasca-Salas C, Fernández-Rodríguez B, Pineda-Pardo JA, Rodríguez-Rojas R, Obeso I, Hernández-Fernández F, et al. Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia. Nature Communications. 2021; 12: 779. https://doi.org/10.1038/s41467-021-21022-9

[160] Bae S, Liu K, Pouliopoulos AN, Ji R, Jiménez-Gambín S, Yousefian O, et al. Transcranial blood-brain barrier opening in Alzheimer's disease patients using a portable focused ultrasound system with real-time 2-D cavitation mapping. Theranostics. 2024; 14: 4519–4535. https://doi.org/10.7150/thno.94206

[161] Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy. 2023; 8: 217. https://doi.org/10.1038/s41392-023-01481-w

[162] Nicholson C, Hrabětová S. Brain Extracellular Space: The Final Frontier of Neuroscience. Biophysical Journal. 2017; 113: 2133–2142. https://doi.org/10.1016/j.bpj.2017.06.052

[163] Konofagou EE. Optimization of the ultrasound-induced blood-brain barrier opening. Theranostics. 2012; 2: 1223–1237. https://doi.org/10.7150/thno.5576

[164] Song KH, Fan AC, Hinkle JJ, Newman J, Borden MA, Harvey BK. Microbubble gas volume: A unifying dose parameter in blood-brain barrier opening by focused ultrasound. Theranostics. 2017; 7: 144–152. https://doi.org/10.7150/thno.15987

[165] Leinenga G, Langton C, Nisbet R, Götz J. Ultrasound treatment of neurological diseases--current and emerging applications. Nature Reviews. Neurology. 2016; 12: 161–174. https://doi.org/10.1038/nrneurol.2016.13

[166] Fishman PS, Frenkel V. Focused Ultrasound: An Emerging Therapeutic Modality for Neurologic Disease. Neurotherapeutics. 2017; 14: 393–404. https://doi.org/10.1007/s13311-017-0515-1

[167] U.S. Food and Drug Administration. Drug Products, Including Biological Products, that Contain Nanomaterials: Guidance for Industry. FDA: Silver Spring (MD). 2024.