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FOCUSED ULTRASOUND

BREAKING BARRIERS IN DRUG DELIVERY, BRAIN THERAPY AND BEYOND

SEPTEMBER 2024

INDUSTRY BRIEF – MEDTECH

Medical Technology

Ultrasound - Breaking barriers in drug delivery, brain therapy and beyond

Due to their ability to treat tissue deep within the body noninvasively and with precision, ultrasound technologies are expanding beyond diagnostics. While High-Intensity Focused Ultrasound has been around for more than 30 years, low- to medium-energy nonthermal applications are showing groundbreaking potential as game-changing alternatives or complements to surgery, drug delivery, radiation therapy, chemotherapy, and cancer immunotherapy. The market is poised for a remarkable annual growth rate of 22%, driven by companies reaching the final clinical validation stage and a dynamic industry landscape that is supported by the financial and strategic backing of established MedTech players. We dive into the key themes and map out leading innovators to keep on the radar.

Ultrasound versatility beyond diagnostics

While diagnostics continue to be the main role of ultrasound technology, Focused Ultrasound (FUS) has emerged as a highly versatile noninvasive procedure for precisely treating tissue deep in the body, It could become a game-changing alternative or complement to surgery, drug delivery, radiation therapy, chemotherapy and cancer immunotherapy. We reveal the diverse mechanisms of actions for FUS and the myriad therapeutic applications that are under research.

FUS as an efficient drug-delivery platform

Despite the evolution of innovative precision medicine, the efficacy of current drug therapies lags, especially in oncology. Although failure to succeed in clinical validation can be due to multiple factors, the specificity of drug delivery plays a vital role in achieving the desired therapeutic effect. Low-medium intensity FUS is being deployed to combat major hurdles in drug delivery, showing outstanding capabilities to increase therapeutic response even when combined with Standard of Care (SOC) therapeutic agents. We highlight EXACT Therapeutics as a novel, drug-agnostic drug delivery platform for cancer treatments, and SonoThera, the world’s first ultrasound-guided nonviral gene delivery platform, which aims to overcome the limitations of other gene therapy approaches.

Temporarily unlocking the blood-brain barrier

While High-Intensity Focused Ultrasound (HIFU) has been around for more than 30 years and has proven its validity for thermal ablation as a treatment in very localised brain diseases, there is much more that can be done. Most of today's research and company focus is on temporarily and safely opening the blood-brain barrier (BBB), as it can unlock a myriad of central nervous system (CNS) therapeutic applications, from efficient drug delivery crossing the BBB bottleneck to easing liquid biopsy. We have identified three players in this space: i) Insightech, which is at the forefront of HIFU in CNS, but also importantly contributing to Alzheimer's Disease efficient drug delivery; ii) Carthera, with its implantable FUS device entering a pivotal phase in Glioblastoma (GBM); and iii) Cordance, developing a diagnostic and therapeutic noninvasive solution.

Histotripsy as nonthermal energy delivery

Focused Ultrasound parameters can be fine-tuned to provide what is known as histotripsy, the only nonthermal energy delivery solution. In contrast to thermal technologies, histotripsy is highly tissue-selective, preventing the ablation from going beyond predefined safe boundaries, and it can be applied in more anatomically challenging structures. With extensive preclinical research being carried out across several cancer types and immunotherapies, we identified two distinctive companies in the frontier of the field: HistoSonics, whose Edison platform received FDA approval for the treatment of liver cancer; and Cardiawave, which is running pivotal studies on the treatment of calcific aortic stenosis.

FUS market to expand at 22% CAGR

With HIFU technologies and microbubble makers leading today's FUS market, we expect it to be boosted by 22% CAGR to reach EUR 1bn by 2029 as Low-Medium Intensity Focused Ultrasound technologies become commercial. We also appreciate the positive contribution of companies whose assets will be categorised as a drug and consequently will be 10x higher priced than today's HIFU tech. While no M&A activity is present, large MedTech players, specifically J&J and GE Healthcare, are supportive of the field, leading several financing rounds and establishing strategic partnerships.

Ultrasound versatility beyond diagnostics

While diagnostics continue to be the main role of ultrasound technology, FUS has emerged as a highly versatile noninvasive procedure for precisely treating tissues deep within the body to become a game-changing alternative or complement to surgery, drug delivery, radiation therapy, chemotherapy and cancer immunotherapy. We reveal the diverse mechanisms of action for FUS and the myriad therapeutic applications that are under research.

Ultrasound is the cheapest and safest diagnostics technology...

Imaging technologies have been at the core of disease diagnostics, aiming at early detection to secure efficient treatment. Computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), ultrasound, and X-ray imaging provide detail of the body's interior that allows clinicians and scientists to conduct in-depth medical analyses. Implementation varies depending on the medical discipline, but it is also limited by the cost and health risks associated with each technology. As it has developed, ultrasound has gained more traction due to less costly portable equipment designs and its safer, noninvasive and nonionizing mechanism of action, expanding into physicians' offices and trauma settings.

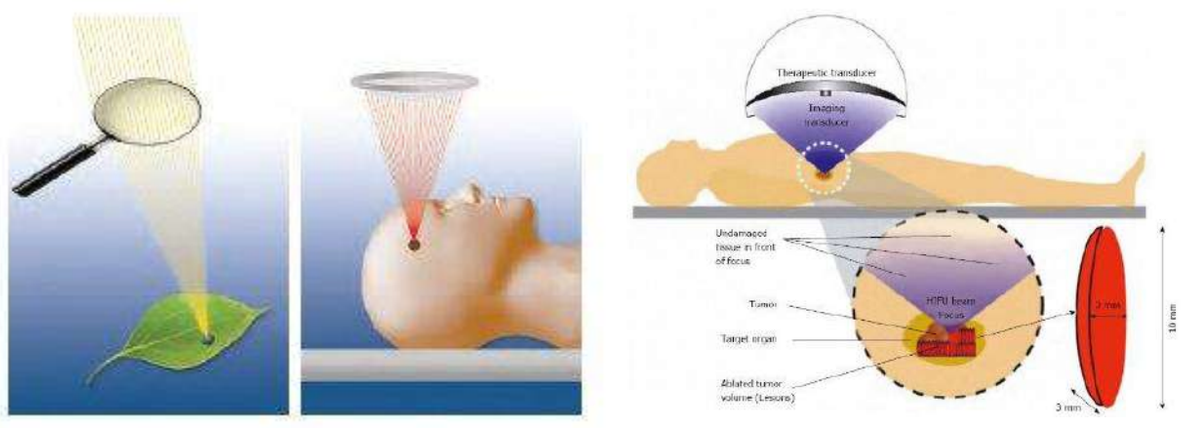
...but also provides a flexible treatment portfolio

While diagnostics continue to be the main role of ultrasound technology, new areas of the therapeutic landscape are being explored, with some granted regulatory approval. **Focused Ultrasound (FUS)** has emerged as a highly versatile noninvasive procedure that aims to precisely treat tissues deep within the body to become a **game-changing alternative or complement to surgery, drug delivery, radiation therapy, chemotherapy and cancer immunotherapy.**

FUS's potential lies in its ability to precisely and non-invasively target deep tissues

The fundamental principle of FUS is like using a magnifying glass to focus sunlight onto a single point to burn a hole in a leaf. In FUS, an acoustic lens is employed to direct multiple intersecting beams of ultrasound towards a precise target deep within the body. The size of this target can range from as small as 1×1.5mm to as large as 10×16mm in thickness x diameter, depending on the design of the lens and the ultrasound parameters. While each individual beam passes through the tissue without effect, their convergence at the focal point generates significant biological effects.

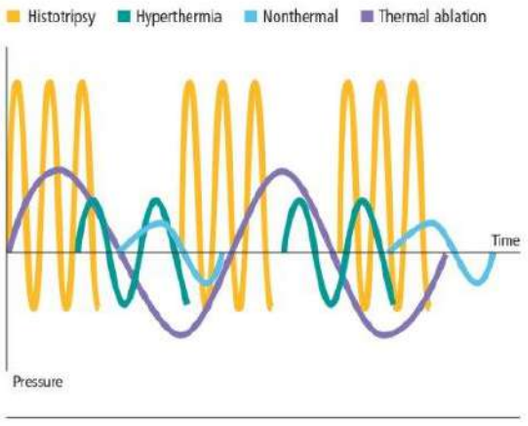
Figure 1 - High Intensity Focused Ultrasound functioning principle



Source: Focused Ultrasound (FUS) Foundation

High-Intensity Focused Ultrasound has been extensively validated in tissue destruction

Figure 2 - FUS MoA



Source: FUS Foundation

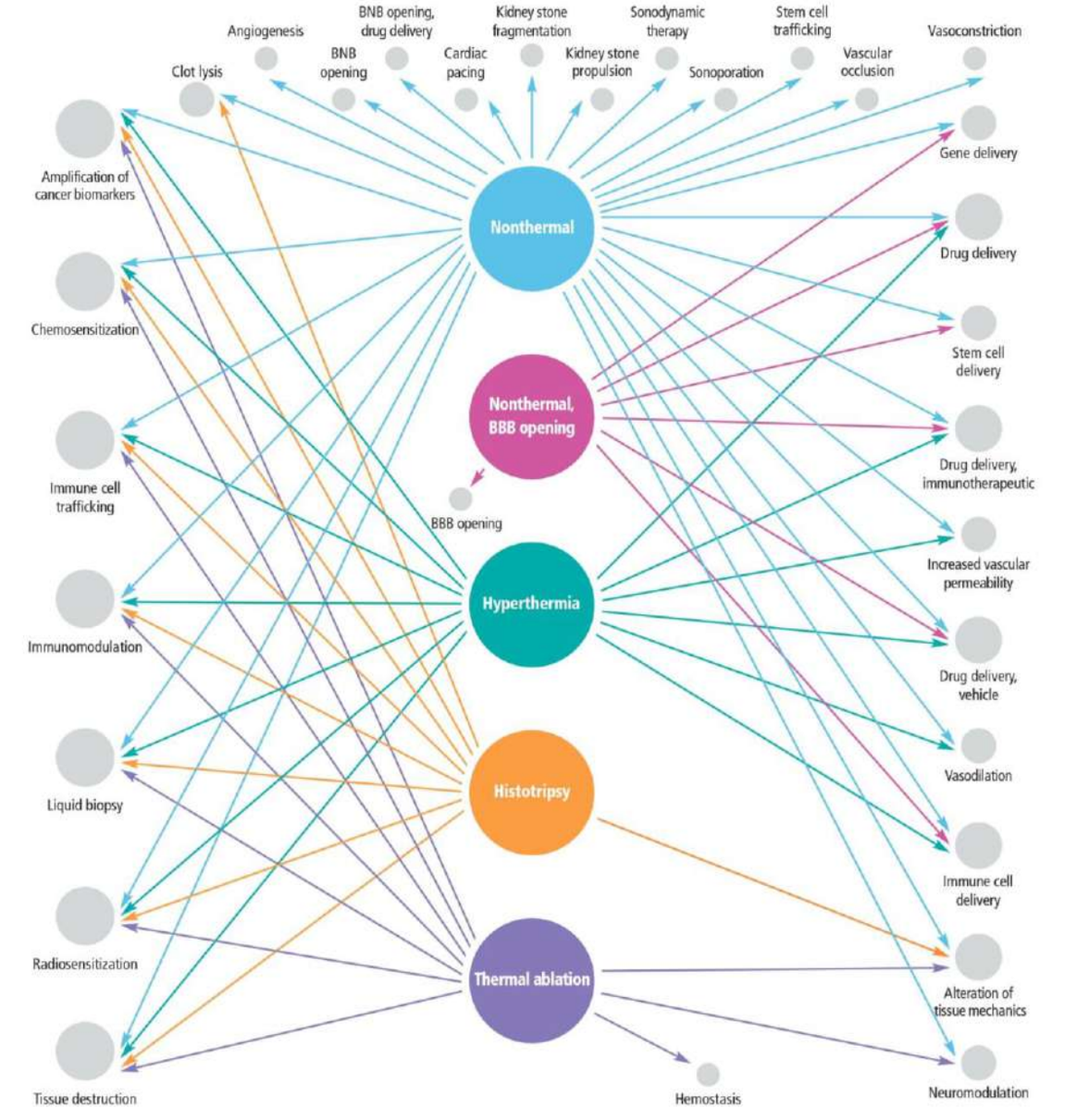
Within the many uses of ultrasound, **High-Intensity Focused Ultrasound (HIFU)** is the most clinically validated, as the only capability with FDA-approved applications up until 2023. Also referred to as **thermal ablation**, it applies high-power continuous-pressure FUS waves, which lead to thermal energy rapidly accumulating at the focal point, denaturing proteins and causing cell death. The FUS duration for irreversible damage varies according to cell type, ranging from one second at 56°C to 4 hours at 43°C. Tissue destruction for tumour treatment is the most common application, especially for gastrointestinal and musculoskeletal indications, followed by the treatment of tremors related to Parkinson's Disease. Despite its proven validity, the high energy accumulation and non-reversible bioeffects limit the technology's therapeutic landscape and target areas.

Emergence of diverse biological responses by fine-tuning the power and mode of FUS application

Given the clear targeting capabilities and safe profile of FUS, new forms of implementation are being explored by varying power, using continuous versus pulsing modes, and adjusting the total treatment time. By applying noninvasive low-power pulsed waves, mild mechanical forces with a transient effect are applied in the tissues. It is within these diverse FUS uses that a myriad of biological effects can be provoked (Figure 3).

- **Nonthermal.** Achieved through applying pulsed waves, a rise in tissue temperature of less than 2°C is sufficient to provoke the desired biomechanical effects on the area of interest. A wide range of biological effects can be triggered. Sonoporation therapy (which increases the permeability of the cell plasma membrane) has gained the most traction as an excellent enhancer for drug delivery.
- **Nonthermal BBB opening.** Following the same principle as nonthermal, FUS can induce raised permeability in the blood-brain barrier (BBB) if applied in a safe noninvasive targeted manner, temporarily opening this naturally tight protective barrier. This process can enhance the delivery of drugs, immune or stem cells, immunotherapeutics, genes, and therapeutic delivery vehicles such as nanoparticles, and therefore has vast therapeutic potential across any brain-regulated disease.
- **Histotripsy.** This leverages the non-thermal, precise effects of FUS to induce tissue destruction by internal cavitation of tissue's endogenous gas. Histotripsy was the first non-thermal mechanism of action (MoA) to be granted FDA approval, with HistoSonics' novel therapy platform Edison approved in late 2023 to treat liver tumours. Depending on the tissue and MoA, the mechanical properties of damaged tissues can also be reverted to a healthy composition. An example is softening calcified heart valves as an alternative to valve replacement.
- **Hyperthermia.** This FUS modality temporarily raises tissue temperature to 42°C, enhancing metabolic activity, and thereby activating radiosensitization, vasolitation, and drug sensitivity. It is being studied to enhance drug delivery in targeted areas that have restricted blood flow, especially tumours, and for immunotherapeutic approaches.

Figure 3 - FUS MoA and biological responses



Source: FUS Foundation

Microbubbles as a vehicle for different therapeutic objectives

Microbubbles (MB) have been used as ultrasound contrast agents for diagnostic purposes for more than two decades, bringing numerous benefits in echocardiography, microcirculatory imaging, and quantitative and molecular imaging. On the therapeutic side, extensive research has been dedicated to bringing versatile groundbreaking applications. While thermal HIFU does not require MB to perform thermal ablation, most nonthermal modalities require MB as enablers of the therapeutic aim. The functions of MB include: i) **vehicles for the required therapeutic agent;** ii) **increasing permeability of the individual cell membranes and the endothelium**, thus **enhancing therapeutic uptake** and locally increasing the activity of drugs; and iii) **easing controlled cavitation** to increase the speed and efficacy of treatment.

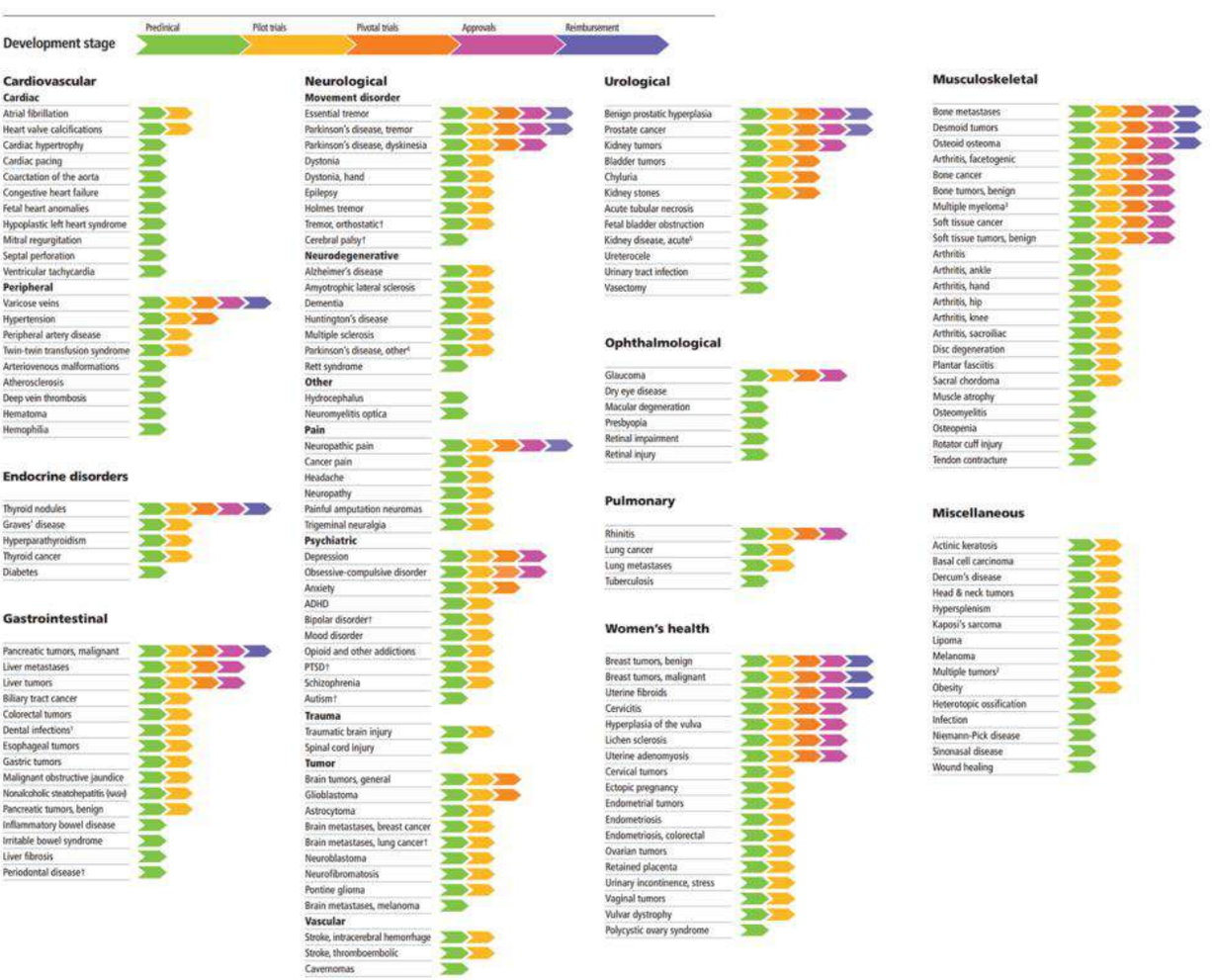
Ranging from proprietary Tx MB design to marketed Dx MB

Depending on the therapeutic aim of the FUS, MB may be highly tailored to ensure efficacy. This tends to be the case with drug delivery platforms. However, other innovators opt for engineering the ultrasound hardware and using microbubbles whose diagnostic use is approved and whose properties may be sufficient to trigger the desired bioeffect. Regardless of the specific FUS use, microbubbles are injected intravenously in the form of a suspension of stabilised microbubbles or liquid droplets, which subsequently vaporise to form a bubble flow through the bloodstream without interfering with the surroundings. Upon the application of FUS, the propagation of a pressure disturbance through a medium at a specific frequency causes the pressure at a given location to fluctuate at that frequency, which causes the microbubbles to oscillate.

A myriad of therapeutic opportunities with multiple pivotal studies seeing the finish line

Considering the high versatility and safe, noninvasive profile of low- to medium-intensity FUS technology, it is not surprising that there is an increasing body of research in this field and a wide therapeutic landscape. Although the industry is still in its initial phase, the emergence of preclinical and proof-of-concept studies has already yielded groundbreaking data across various fields, pushing therapeutic FUS from a less clinically focused to a commercially relevant sector. **With the first non-thermal FUS approval in late 2023, we believe now is the perfect time to explore the diverse trends and identify the innovations that will drive market expansion in the coming years.**

Figure 4 - State of research and regulatory approvals by body system



Source: FUS Foundation

FUS as an efficient drug-delivery platform

Despite the evolution of innovative precision medicine, the efficacy of current drug therapies lags, especially in oncology. Although failure to succeed in clinical validation is a multifactor challenge, specificity in drug delivery plays a vital role to elicit a drug's intended therapeutic effect. Low-Medium Intensity Focused Ultrasound is being deployed to combat major hurdles in drug delivery, showing outstanding capabilities to increase therapeutic response also when combined with SOC therapeutic agents. We highlight EXACT Therapeutics as a novel drug-agnostic drug delivery platform for cancer treatment, and SonoThera, the world's first ultrasound-guided nonviral gene delivery platform, which aims to overcome the limitations of other gene therapy approaches.

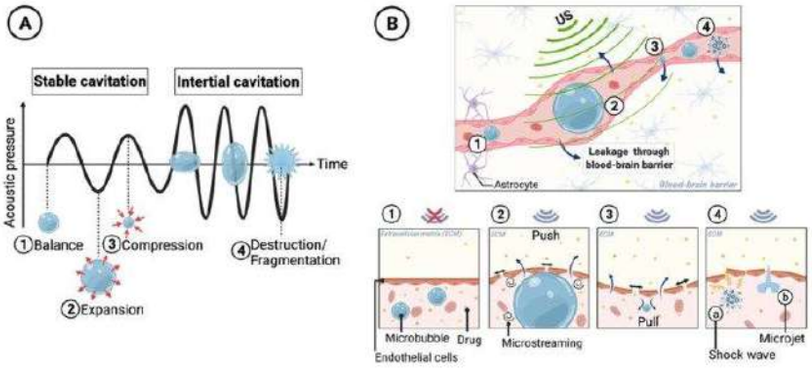
Delivering drugs remains a hurdle in Oncology

90% of drugs under development fail during early clinical trial phases, with over 50% of failures attributed to a lack of efficacy. This is particularly evident with anti-cancer agents, which typically show promising preclinical results but encounter complex barriers to efficacy during clinical translation. While multiple factors can contribute to the lack of effectiveness in early-phase oncology trials, there is substantial evidence that suboptimal drug delivery and inadequate penetration of drugs into solid tumours are significant contributors. This can be a result of resistance created by natural protective barriers in the tumour microenvironment (TME), which tends to prevent large molecules from crossing the cell membranes, impeding impacts in the targeted area (San 2022, Pan 2020).

Non-thermal FUS as a means to cross biological protective barriers

Among the many FUS MoAs, non-thermal FUS or Ultrasound-mediated Microbubble (USMB) are among the most promising for modifying the permeability of cell membranes and enhancing the absorption of these molecules. When ultrasound waves of the correct frequency are applied in the targeted area, the microbubbles (MB) that were co-administered with the therapeutic agent undergo rapid expansion and contraction. The process is initiated by low-intensity FUS waves, where MB undergo slight oscillations in size, leading to stable cavitation. The slight MB compression and expansion interferes with the endothelium membranes, causing a temporary increase in the gap–junction distance between vascular endothelial cells, thereby allowing circulating therapeutic agents to extravasate. Following this, higher wave intensities are applied, causing the MB to undergo unstable growth and internal cavitation, followed by rapid collapse and implosion.

Figure 5 - Non-thermal FUS mechanism of therapeutic administration through endothelium



Source: Barzegar-Fallah 2022

Extensive preclinical data validates sonoporation to deliver oncology drugs

The cavitation phenomenon, or sonoporation therapy, and its ability to increase drug uptake, have been extensively covered in a broad range of preclinical trials, showing marked progress in treating bladder, breast, cervical and prostate cancer. (Chen 2013). As well as improved drug efficacy, when combined with radiotherapy, USMB allows for the administration of low radiation doses that can elicit a similar effect observed with single high doses of radiation. This is due to the activation of specific genetic pathways involving primarily endothelial cells. Similarly, the risk of chemotherapeutic drug toxicity is reduced in combination with USMB, as lower drug concentrations are required to elicit the effect.

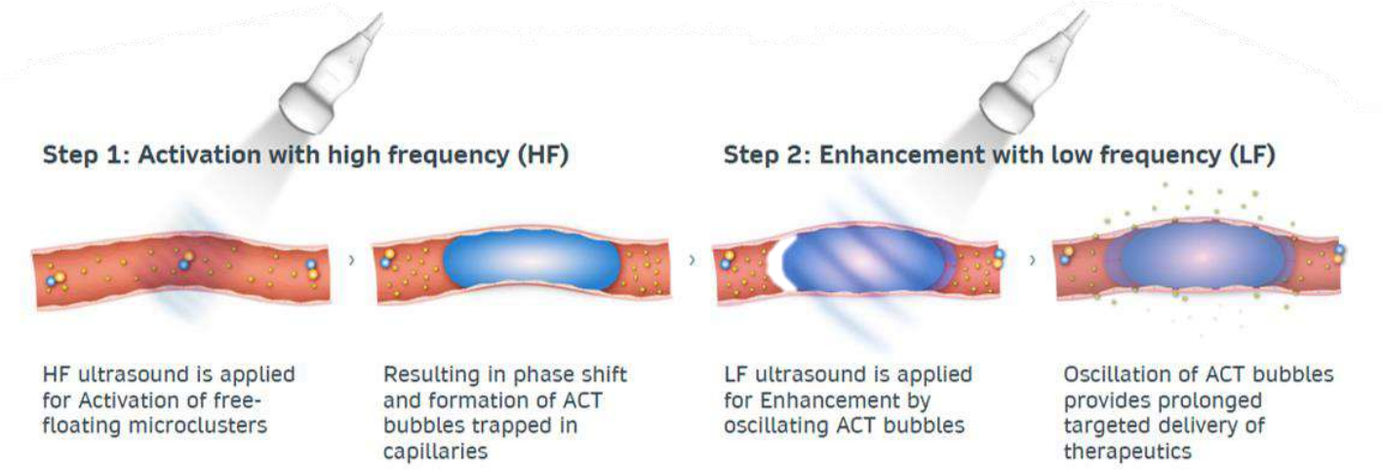
EXACT Therapeutics has a unique drug-agnostic delivery platform

Because the field is still in an early stage, no therapeutic USMB product has yet gained market clearance. We have dived into the sector to look for the most advanced and differentiated players. On the back of supportive and distinctive preclinical data, we have identified EXACT Therapeutics.

- EXACT Therapeutics has developed **Acoustic Cluster Therapy (ACT),** a unique drug-agnostic ultrasound-mediated microbubble platform, whose efficacy in drug delivery relies on its **proprietary microbubbles and microdroplets - PS101.**
- While based on the principle of sonoporation, the MoA of ACT MBs varies slightly, hence the term ACT (see Figure 7). Instead of undergoing the phases of stable and inertial cavitation, causing holes in the cell membranes upon FUS application, MBs expand, forming a large bubble that stabilises within the blood vessel, leading to oscillations. The oscillations act as a pump, enhancing the entrance of the coadministered drug through the expanded capillary wall in which the cell's gap junction has been increased.
- ACT treatment is administered by using a customised ultrasound probe that is compatible with conventional ultrasound hardware, thus simplifying the R&D process and commercial adoption. Additionally, the proprietary ACT MB, PS101, enabled the creation of a versatile drug-agnostic platform, as it is co-administered with commercial drugs without the need for reformulation. We view this as a clear competitive advantage as will enable the company to ramp up its portfolio whilst reducing R&D costs.
- **Since the company spun out of GE Healthcare** to develop and commercialise, the drug delivery efficacy of ACT treatment has been validated across **numerous preclinical cancer models** (pancreas, breast, colon, prostate, brain), all showing **raised treatment efficacy** when the drug delivery was enhanced with ACT vs. SOC alone.
- Outstanding drug delivery capabilities were also shown in the **phase 1 trial evaluating ACT treatment of liver metastasis. Compared to the baseline, the average percentage shrinkage of ACT-treated liver tumours was >10x than seen in control tumours** where ultrasound was not applied to enhance the drug delivery (access results here).
- Given the versatility of ACT treatment and proven efficacy across several cancer types in preclinical/clinical studies, the company aims to first bring to market ACT treatment in pancreatic cancer as being a clear high unmet need with the option for orphan drug designation, allowing higher pricing.

- The company plans to initiate the **ENACT phase 2 study in first-line treatment of locally advanced pancreatic cancer in combination with SOC chemotherapies in H2 2024**, with an expected interim readout in 2025. Other preclinical studies include GBM, for which it has partnered with **Cordance Medical**, and **Immunotherapy** drug delivery applications.

Figure 7 - Proprietary ACT Therapy developed by EXACT Therapeutics



Source: EXACT Therapeutic

Gene therapies also lack a competitive delivery method

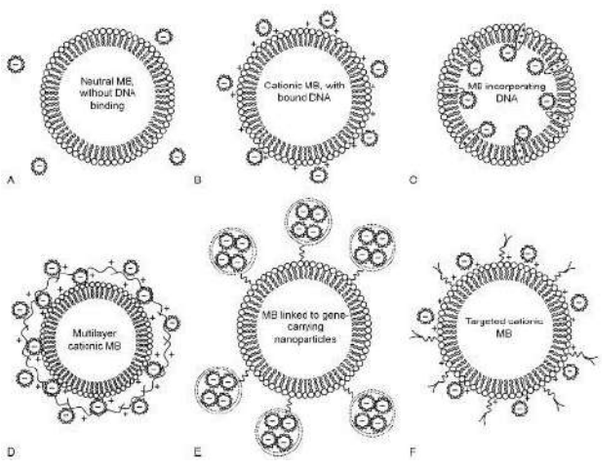
Although most clinical efforts have been directed towards the delivery of oncology drugs, an increasing interest has emerged in how FUS could also benefit gene therapy delivery. Available gene delivery methods can be broadly divided into:

- **Cell-mediated methods,** which primarily rely on administering cells that were transfected in vitro with a transgene and then implanted in vivo to deliver the therapeutic protein. Although this method may be more efficient and enable better control of transfection in specific cells, it is more complex and less cost-effective than in vivo delivery, due to the prolonged time and resources required for cell harvest and expansion in vitro.
- The **direct method uses** viral and **nonviral vectors** to deliver the transgene to the target tissue or cells in vivo. The use of viral vectors is deemed more efficient but less safe than nonviral methods, mainly due to possible immune reactions to the viral proteins and the potential for cell transformation and vector genome mobilisation. Nonviral delivery therefore appears to be a safer, simple and cost-effective method for in vivo delivery when short-term expression of a transgene is required, making it a leading candidate for clinical translation. However, nonviral delivery methods are mainly limited by their relatively low efficiency of transfection compared with viral vectors.
- **Electroporation** uses needle electrodes to create electrical pulses in the target tissue with improved efficiency. The need for electrodes limits the use of electroporation to targets that are close to the skin.

Sonoporation therapy opens a new research paradigm in gene administration

Given the pros and cons of each delivery method, ultrasound-mediated gene delivery has become an increasingly attractive research field. Using sonoporation, most preclinical studies are focused on coadministering commercially available Dx MB with the therapeutic genetic material to be delivered, most commonly plasmid DNA. Despite proving to be a less invasive method, in most cases it required higher doses of genetic material for successful transfections, as a large part of the administrated DNA was rapidly degraded through endogenous nucleases (Lentacker 2006). To improve gene delivery efficiency at the sonoporation site, different angles are under research including: i) MB type and their way of binding to the genetic material (see Figure 8); and ii) ideal power setting and duration of ultrasound exposure (Panje 2013).

Figure 8 - Different strategies for ultrasound-mediated gene delivery using various types of microbubbles (MB).



(A) Neutral MB coadministered with therapeutic genetic material without direct interaction between them. Alternatively, MB can act as intravascular transporters of genetic cargo, where therapeutic genetic material can be charge-coupled onto the surfaces of cationic microbubbles (B), or directly integrated into the microbubble shell or core during synthesis (C). To increase the therapeutic payload of gene-carrying MB, strategies include MB with multiple layers of a cationic polymer on the shell surface (D) or the use of gene-complexing nanoparticles that are then linked to the surface of MB (E). (F) Gene-carrying microbubbles can also be molecularly targeted by adding binding ligands (eg, antibodies [Y shapes] or small peptides) onto the microbubble shell.

Source: Panje 2013

SonoThera is a pure-play gene therapy R&D house

Within the ultrasound gene-delivery landscape we identified preclinical-stage SonoThera as a relevant name to keep on our radar. The company **aims to develop the world's first ultrasound-guided nonviral gene delivery platform,** which overcomes the limitations of other gene therapy approaches. While public information is limited, with only a few posters on preclinical data presented at the American Society of Gene and Cell Therapy held in May 2024, the company seems well-backed from an investor standpoint and with relevant partnerships in place.

SONOTHERA™

Private, US, founded in 1982
EUR 56m raised to date
Last round: Series A, April 2022, EUR 56m
Backed by J&J, Eli, Lilly and Company, ARCH Venture Partners
29 employees

SonoThera platform
Ultrasound-guided nonviral gene therapy

- Sonothera has licence agreements in place with the most relevant MB developers, Bracco and Lantheus Imaging, allowing the use of their MB tech in the development of SonoThera's platform.
- On the R&D side, Sonothera joined forces with Janssen to develop a novel approach for delivering nucleic acid-based therapeutics. The research will focus on the delivery of next-generation DNA and RNA-based nucleic acid therapeutics to non-liver organ targets and diseases.
- **J&J Innovation**, along with ARCH Venture Partners, Eli Lilly and Company, among others, led the Series A USD 60m Series A funding, which closed in April 2022.

Temporarily unlocking the blood-brain barrier

While High-Intensity Focused Ultrasound (HIFU) has been around for more than 30 years and has proven its validity for thermal ablation as a treatment in very localised brain diseases, there is much more that can be done. Most of the research and company focus today is on temporarily and safely opening the blood-brain barrier (BBB), as this can unlock a myriad of central nervous system (CNS) therapeutic applications. This includes efficient drug delivery by overcoming the BBB bottleneck and facilitating liquid biopsy. We identified i) Insightech at the forefront of HIFU in CNS, but also an important contributor to efficient drug delivery in Alzheimer's Disease; ii) Carthera, with its implantable FUS device entering a pivotal phase in Glioblastoma (GBM); and iii) Cordance, developing a noninvasive diagnostic and therapeutic solution.

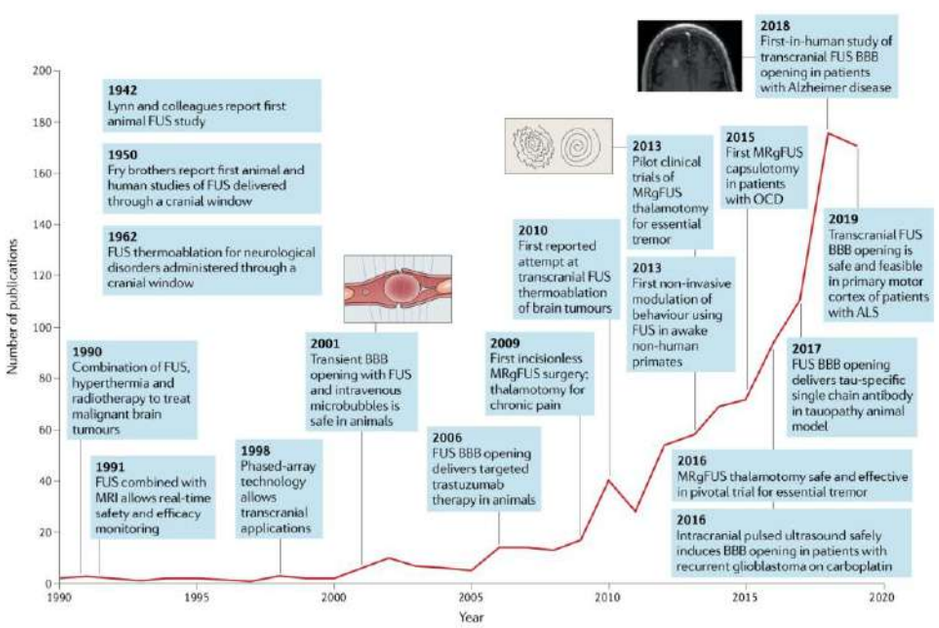
High-intensity ultrasound use is limited to tissue destruction

In the context of targeting the CNS, HIFU is a well-established technology. It enables a nonreversible thermal transcranial treatment for a range of neurological motor disorders where tissue ablation is an effective therapy option. These include Parkinson's Disease tremors, essential tremors and neuropathic pain. While HIFU has proven its validity in cases where a very small area requires ablation, there still exist critical challenges in addressing CNS disease, where other forms of FUS can be of exceptional potential.

Increasing research in targeting the brain through nonthermal FUS

The first preclinical use of Nonthermal-Focused Ultrasound dates back to 2001, proving it to be safe for temporarily opening the blood-brain barrier (BBB) to sequentially facilitate drug delivery (see Figure 10). This is a major research focus in the field, as it can unlock numerous promising therapies for the CNS. **Neuromodulation applications are also under research**, although they are still in the preclinical stage.

Figure 10 - Clinical research in FUS for brain applications



Source: Meng 2020
ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier;
MRgFUS, magnetic resonance-guided FUS; OCD, obsessive-compulsive disorder.

Table 1 - FUS applications in the brain

FUS Intensity	Effect	Mechanism	Examples of Applications	Companies	Development stage
High	Thermal, irreversible tissue destruction (ablation)	Coagulative necrosis	Essential Tremor, PDs tremor, neuropathic pain, among others	InsigthTec	Commercial
Medium	Mechanical, transient opening of the BBB	MB stable oscillation leads to shear stress, direct interactions	Enhanced delivery of antitumor agents, gene therapy, and cells for the treatment of a wide range of CNS diseases. Applicable for liquid biopsis.	Carthera InsighTec Cordance Medical	Clinical
Low	Mechanical, neuromodulation (stimulation and suppresion)	Thought to be related to mechanical perturbation of voltage-dependent ion channels or changes in bilayer impedance	Activation of motor response, suppression of VEO, acute epileptic activity	Stanford University Oxford University	Preclinical

Source: BG IRIS, Fishman 2017

The blood-brain barrier blocks 98% of small molecules

The blood-brain barrier is a key feature of the vasculature of the brain and consists of a layer of endothelial cells sealed together by specialised cell-cell junctions and supported by other cell types. The tight control of transport in both directions prevents the entry of most substances from the systemic blood supply, including leukocytes, into the brain, which helps maintain the physiological conditions required for neural signalling, and shields neural tissues from neurotoxins in the blood. Unfortunately, the **BBB also acts as the major bottleneck in drug delivery** to treat diseases in the CNS. Research indicates that 100% of large molecules cannot access the BBB, while 98% of small-molecule drugs, and all biologics, cannot pass through the BBB into a non-disrupted brain unaided (Pardrige 2005). This presents a significant barrier to delivering a meaningful concentration of drugs to treat neurological diseases, including psychiatric diseases, neurodegenerative diseases, brain cancers, and strokes.

FUS can temporarily open the BBB

The combination of FUS and MB has been shown to **non-invasively, reversibly and safely open the BBB** to facilitate the delivery of macromolecular therapeutic drugs such as monoclonal antibodies, genes and chemotherapies into the brain parenchyma in animal models (Kinoshita 2005, Treat 2012, Burgess 2012). The ability to focus the US beam down to the millimetre scale provides much more spatiotemporal precision and control than alternative approaches, such as co-administration of vasodilators or hyperosmotic agents or Trojan horses, while limiting the risk of off-target adverse effects in the brain. Additionally, FUS therapy can be precisely fine-tuned in real time when combined with stereotactic image guidance or acoustic emission.

Safety must be ensured through proprietary hardware

The FUS MoA principle of temporarily opening the BBB relies on the same principle as opening the tumour microenvironment (TME) through sonoporation. The same acoustic pressure waves that interact with the microbubbles amplify their oscillations, generating microstreaming fluid flow and increasing shear stress in the surrounding area. This process temporarily and safely disrupts the integrity of the BBB endothelium, allowing both endogenous and exogenous molecules to pass through. However, **applying transcranial FUS involves complexities vs. applying it directly over soft tissue** due to substantial attenuation and distortion when crossing tissues of different densities. This results in low pressures reaching brain tissue and phase aberration, which can shift the target region (Krishna 2018). FUS BBB innovators have had to consider hardware design within their offering to comply with the efficacy and safety in brain applications, in addition to MB and power and duration of therapy.

An implantable FUS device to treat a wide range of brain disorders

Carthera **is among the most advanced players the FUS-mediated BBB opening landscape**, targeting numerous critical CNS indications with SonoCloud, its proprietary implantable FUS device.

CARTHERA
Advanced Brain Therapy

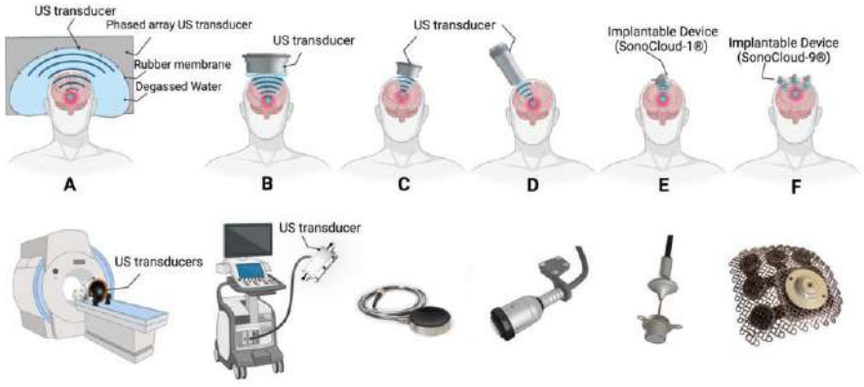
Private, France, founded in 2009
EUR 82m raised to date
Last round: Series B, Jun 2023, EUR 42m
Backed by Unorthodox Ventures, Supernova Invest, Panakes partners
20 employees

SonoCloud

Implatable FUS device for BBB opening
GBM pivotal study ongoing
AD ph1/2 study completed

- The SonoCloud device tackles FUS-skull transmission complexity by directly bypassing the skull, as it is installed through a cranial window and affixed rigidly, allowing the repeated precise delivery of ultrasound to the same location, and is compatible with higher frequencies (~1 MHz).
- Carthera has developed **two MRI-compatible versions of SonoCloud,** including the SonoCloud-1 and SonoCloud-9 devices, which vary in the number and size of ultrasound emitters included (1 and 9 respectively, see Figure 11). Both are designed to disrupt large regions of the BBB to increase the therapeutic efficacy of drugs in targeted brain regions and are currently in clinical trials for glioblastoma (GBM), brain metastases, and Alzheimer's Disease.
- **SonoCloud-9 in GBM is progressing through the latest stages of clinical validation** as it is recruiting 560 patients across 40 sites in Europe and the US. The open-label, comparative pivotal trial will evaluate overall survival in patients undergoing carboplatin chemotherapy and treated with the SonoCloud-9 system to open the BBB. This will be compared to the standard of care (lomustine and temozolomide) in patients with the first recurrence of GBM.
- Outstanding results were reported from the Phase I/II study with BBB opening primary endpoint met, with 90% of emitters showing BBB disruption after FUS application (here).
- The innovativeness and clear unmet need of SonoCloud-9 for the treatment of GBM are backed by i) **Breakthrough Device Designation (BDD)** granted by the FDA; and ii) **Orphan Drug Designation**, granted by FDA and EMA.

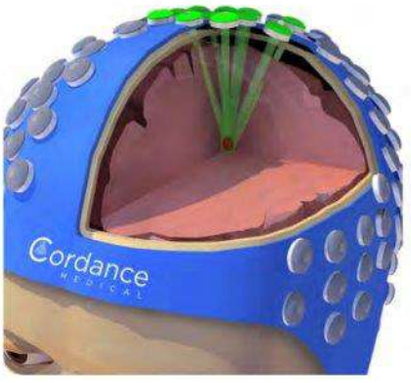
Figure 11 - FUS designs for brain applications



(A,B) Extracranial hemispheric focused ultrasound arrays (multi-element devices, ExAblate and NaviFUS, respectively). (C) Extracranial mono-element focused device. (D) Transcranial Pulse Stimulator with real-time tracking system (TPS, NEUROLITH). (E) Implantable, unfocused single-emitter ultrasound device (SonoCloud-1). (F) Implantable, unfocused nine-emitter ultrasound device (SonoCloud-9).

Source: Barzegar-Fallah 2022

Figure 12 - Cordance's NeuroAccess platform



Source: Cordance Medical

NeuroAccess transcranial helmet granted BDD in liquid biopsy in brain tumours

Cordance MEDICAL

Private, US, founded in 2018
EUR 5.10m raised to date
Last round: Early VC, EUR 3m
9 employees

NeuroAccess for BBB opening
SonoBiopsy for liquid biopsy
GBM clinical feasibility study
SonoScript for drug delivery
Preclinical in GBM, AD, PD

Cordance's BBB opening approach relies on a portable noninvasive FUS device that uses a pre-acquired image and neuronavigational positioning system that allows for accurate treatment without the need for real-time imaging. NeuroAccess operates in a lower frequency regime and is being evaluated for diagnostics and therapeutic approaches that benefit from FUS-mediated BBB opening. Its most **clinically advanced application is liquid biopsy for brain tumours, which has been granted BDD by the FDA** and is currently being evaluated in feasibility studies. In this segment, NeuroAccess directly competes with the HIFU leader, InsighTec, which is currently running an international, multisite clinical trial (here). The rationale for implementing FUS for liquid biopsy is strongly backed by: i) the invasiveness and risks of SOC; and ii) preliminary studies showing FUS as a safe and efficacious method for opening BBB, increasing tumour biomarkers in the peripheral bloodstream that can then be easily measured. More tailored therapies through FUS-mediated drug delivery can then be provided. We note that **Cordance and EXACT Therapeutics set up a partnership to combine their respective expertise**, access through BBB and efficient drug delivery through proprietary MB, to deliver more efficient therapies into the brain.

Insightec advancing in Alzheimer's drug delivery enhancement

INSIGHTEC

Private, Israel, founded in 1999
EUR 505m raised to date
Last round: VC, June 2024, EUR 150m
Backed by Ally Bridge Group, Nexus Neurotech' and Fidelity
410 employees

Exablate
HIFU in Essential Tremor and PD approved
Low FUS liquid biopsy pivotal study
Low FUS AD FiH study

Numerous trials have evaluated the safety and efficacy of opening the BBB by using low-intensity FUS for Alzheimer's therapy applications (see Table 2). Insightec's Exablate system is being used across all relevant studies as it enables precise MRI guidance to track the therapy response while applying a low-intensity 220 kHz FUS transducer. A First-in-Human (FiH) trial is currently assessing whether BBB opening in combination with a standard-of-care anti-amyloid-beta monoclonal antibody treatment can accelerate the clearance of amyloid-beta plaques in the brains of patients with Alzheimer's disease. **Initial preliminary results** published on January 2024 in the New England Journal of Medicine indicate **safe BBB opening and restoration as well as a measurable average of 32% greater reduction in amyloid-beta plaques in brain areas with BBB opening compared to areas with no opening** (access here).

Table 2 - BBB opening in Alzheimer Disease patients

Authors	Trial Dates	Target	Volume of Tissue for BBB Opening	Safety Results	Other Pertinent Findings
Mehta 2021	Oct 2018 May 2019	The hippocampus was the targeted region, with three target locations for each subject within two weeks.	The volume for each target location was 5 × 5 × 7 mm.	No adverse effects were observed, and BBB closing occurred within 24 h.	Enhancement was observed in the downstream veins from the target location.
Mehta 2023	Nov 2019 July 2022	The hippocampal, parietal, and frontal regions of the brain. There were 77 target sites in total among the participants.	Treatment volume varied between the different brain locations.	BBB closure occurred within 24 and only minor adverse effects were detected, with no severe hemorrhages.	There were alterations to the downstream veins from the treatment sites.
Lipsman 2018	March - Sept 2023	Right frontal lobe	Target locations were about 9 mm × 9 mm, in a 3 × 3 grid	No significant adverse effects or cognitive decline within three months post-treatment	There was no change in amyloid-beta volume in the patients post-treatment.
Rezai 2020	Not provided	The hippocampus and entorhinal cortex. BBB opened between 14 and 71% of the hippocampal volume.	The total volume opened per patient ranged from 318 mm3 to 873 mm3.	No adverse effects, hemorrhaging, or cognitive decline were observed. BBB was effectively opened and safely closed within 24 h of the intervention.	There was no area outside of the targeted region that was exposed to BBB opening.
Rezai 2024	Not provided	Nondominant frontal lobe, parietal, temporal lobes and hippocampus in different patients. Six treatments over 26 weeks.	Opening of 10 cm3 in the first patient, 20 cm3 in the second and 40 cm3 in the third.	No adverse events, BBB opened and restored within 24–48 h.	Treated with aducanumab, average of 32% amyloid beta reduction in treated regions after 26 weeks

Source: Durham 2024, BG IRIS

Histotripsy as nonthermal energy delivery

Focused Ultrasound parameters can be fine-tuned to provide what is known as histotripsy, the only nonthermal energy delivery solution. In contrast to thermal technologies, histotripsy is highly tissue-selective, preventing the ablation from going beyond predefined safe boundaries and it can be applied in more anatomically challenging structures. With extensive preclinical research being carried out across several cancer types and immunotherapies, we identified two distinctive companies in the frontier of the field. HistoSonics, whose Edison platform received FDA approval for the treatment of liver cancer; and Cardiawave, which is running pivotal studies on the treatment of calcific aortic stenosis.

Thermal-based ablation heating risks limit its extended application

Thermal-based ablations, commonly performed percutaneously under image guidance, encompass techniques such as radiofrequency ablation, microwave ablation, and cryoablation. These methods work by heating or freezing targeted tissues to induce necrosis. However, they are limited by the heat sink effect, where blood flow reduces the ablation zone, making margin prediction challenging and heavily dependent on physician skill. Moreover, thermal spread restricts the treatment of tumours located near sensitive structures. High-Intensity Focused Ultrasound (HIFU) represents a noninvasive alternative. However, it still shares the same shortfalls as other thermal ablation methods, with clinical application remaining limited due to anatomical challenges and lengthy procedure times.

Histotripsy emerges as a nonthermal ablation alternative…

Histotripsy has emerged as an alternative FUS ablation technology to HIFU, whose MoA relies on mechanical instead of thermal tissue modifications. While HIFU generates continuous and long high-intensity waves to heat the tissue, histotripsy uses **short US bursts of low-duty cycles, thus avoiding heating, yet at higher peak pressure amplitudes, which trigger acoustic cavitation of the endogenous gas in tissues.** Upon the application of multiple cycles, the microbubbles, in this scenario created by the endogenous gas, undergo rapid expansion and compression, triggering high strain and stress in the adjacent cells resulting in the mechanical disruptions of the therapeutic aim.

…with high tissue selectivity and predictability

The **histotripsy power and frequency setting required to lead to ablation largely vary according to the tissue of application** as tissues have specific resistance thresholds. For instance, strong collagen tissues such as large vessels, nerves and stroma have higher tensile strength and smaller endogenous microbubbles when compared to parenchymal structures such as solid organs or tumours. It therefore takes more histotripsy cycles to liquefy collagen-based tissue than non-collagenous tissue. Such selectivity is a key competitive advantage in using histotripsy vs. HIFU as the tissue of interest can be safely ablated while the surrounding tissues' mechanical composition is not triggered by those ultrasound parameters. For instance, when treating the kidney, renal cortical tissue can be completely liquefied, while the collecting system remains structurally intact (Longo 2019).

Extensive preclinical research across cancer types and immunotherapies

Histotripsy is showing promise in a variety of pre-clinical applications. These include the treatment of tumours in the liver, kidney and prostate, as well as neurological diseases, thrombosis, hematomas, neonatal and fetal congenital heart diseases, valvular diseases, kidney stones, abscesses, tendons, and biofilms. Among these, **liver cancer** treatment has been the first indication to have been granted FDA approval, while the use of histotripsy for the **treatment of calcific aortic stenosis** is undergoing pivotal studies.

The first FDA-approved nonthermal ablation technology in liver cancer

In late 2023, HistoSonics brought to market the first histotripsy-based ablation technology, *Edison platform*, with liver cancer as its initial therapy.

HISTOSONICS

Private, US, founded in 2009
EUR 194m raised to date
Last round: VC, Dec 2022, EUR 85m
Backed by J&J, Yonjin Venture, Gary Comer, Venture Investors, Lumira Ventures
166 employees

Edison platform
Histotripsy for liver cancer - FDA approved in Oct 2023
Ongoing kidney studies

- The **system was first evaluated in benign prostatic hyperplasia** in a phase I study across 2 US medical centres (n=25) in 2016-2017 (NCT01896973). While safety was demonstrated, the device did not demonstrate efficacy in tissue disruption with results being similar to those of patients treated with oral medication. Results indicated that major tissue-specific adjustments would be needed to provide the ablation intended.
- The company then proceeded to test its device on **hepatic histotripsy in noncurative patients with multifocal malignancy in a phase I study** (n=8) where initial safety and efficacy were proven (NCT03741088). Eleven liver tumours, including one hepatocellular carcinoma and ten metastases from colorectal, breast, and gallbladder cancers, were treated. The primary endpoint of achieving planned ablation was confirmed by MRI in all but one case, where a small tumour was mistargeted due to ultrasound imaging limitations. No significant procedure-related adverse events were reported. MRI results showed local tumour regression, with the ablation zone's volume contracting by 36.0% at one week, 53.6% at one month, and 71.8% at two months. Additionally, two patients experienced a continuous decline in tumour markers, with one patient showing shrinkage of non-target tumours, suggesting a potential abscopal effect.
- Edison Platform was **granted BDD by the FDA in 2021** and **regulatory approval in October 2023** for the treatment of liver cancer on the back of #HOPE4LIVER US and EU pivotal studies as showing successful treatment efficacy (NCT04572633, NCT04573881).
- Although no clear pipeline is shared by the company, other ongoing clinical studies include primary solid renal tumours (NCT05432232).
- We note that the company is **strongly backed by J&J** as it led the last financing round of USD 85m in December 2022. Yonjin Venture, Gary Comer, Venture Investors, Lumira Ventures and the State of Wisconsin Investment Board also participated in the round.

Restoring softness in calcified heart valves through noninvasive nonthermal ablation

CARDIAWAVE

Private, France, founded in 2014
EUR 21m raised to date
Last round: Series B, Sept 2022, EUR 2.45m
Backed by MedTech Innovator, Angels Santé
35 employees

VALVOSOFT
Histotripsy for calcific aortic stenosis pivotal studies ongoing

While ablation through liquefying soft tissue may have broader application potential in cancer, histotripsy can also be employed to restore lost mechanical properties on soft tissues that are crucial to ensure healthy functioning. Results can be obtained by fine-tuning the range of pressures and pulse durations. The first and most advanced clinical application under evaluation is the treatment of calcific aortic stenosis, where calcific deposits on valve leaflets restrict their mobility. With current treatments limited to invasive surgical interventions, specifically aortic valve replacement or transcatheter aortic valve replacement (TAVR), Cardiawave is at the frontier of using histotripsy to restore the mechanical healthy behaviour of the valves. **Safety and efficacy were validated in 40 patients** suffering from severe aortic stenosis who were treated across **two FiH clinical studies** across France, the Netherlands and Serbia (here). The therapy is **currently running pivotal studies** whose enrolment concluded in February 2024.

FUS market to expand at 22% CAGR

With HIFU technologies and microbubble makers leading today's FUS market, we expect it to be boosted by 22% CAGR to reach EUR 1bn by 2029 as Low-Medium Intensity Focused Ultrasound technologies become commercial. We also appreciate the positive contribution of companies whose assets will be categorised as a drug and consequently be 10x higher priced than today's HIFU tech. While no M&A activity is present, big MedTech players, J&J and GE Healthcare, are supporters of the field, leading several financing rounds and establishing strategic partnerships.

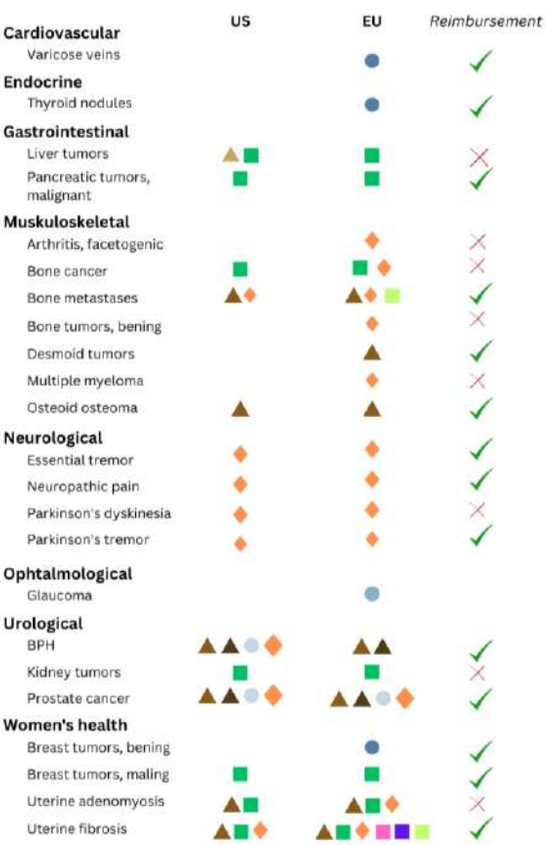
The therapeutic FUS market is today led by HIFU and microbubble developers

Today's Therapeutic Focused Ultrasound marketed solutions rely on well-established High-Intensity Focused Ultrasound (HIFU) technologies with thermal ablation as the main clinical application across neurological disorders. The market around microbubbles is used equally for diagnostic and therapeutic purposes. To date, 31 medical applications have been approved worldwide. Of these, only 15 are FDA-approved and 23 are CE-marked, with HistoSonics being the only nonthermal FUS technology to gain FDA approval (see Figure 18)

Figure 17 – Commercial FUS companies

Source: BG IRIS, FUS Foundation

Figure 18 - FUS regulatory approvals and reimbursement per company across US and EU

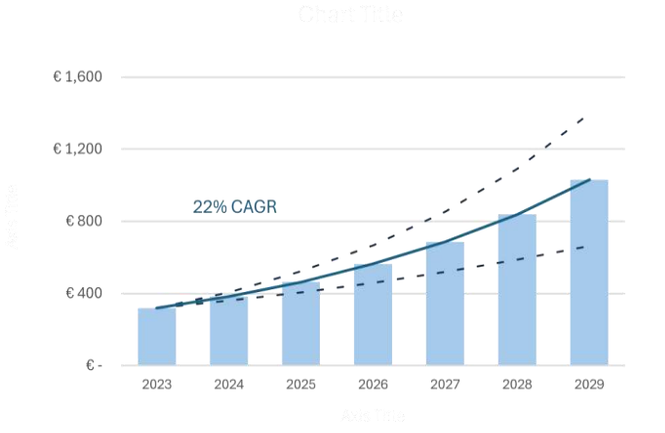


Source: BG IRIS, FUS Foundation

Nonthermal FUS to boost the market to EUR 1bn by 2029

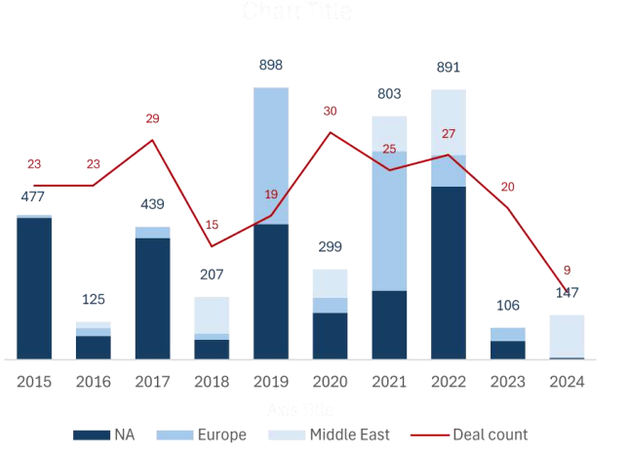
Estimates indicate a value of EUR 380m as of 2023, which is expected to be boosted at a 22% CAGR from 2023 to 2029, reaching EUR 1bn. We consider that estimate as conservative given the **enormous therapeutic potential** of **Low-Medium Intensity Focused Ultrasound**, the number of companies already reaching the final steps of clinical validation, along with the potential drug pricing associated with drug delivery platform solutions.

Figure 19 - FUS market projected revenues (M)



Source: BG IRIS

Figure 20 - Capital raised (EURm) FUS market



Source: BG IRIS, Pitchbook

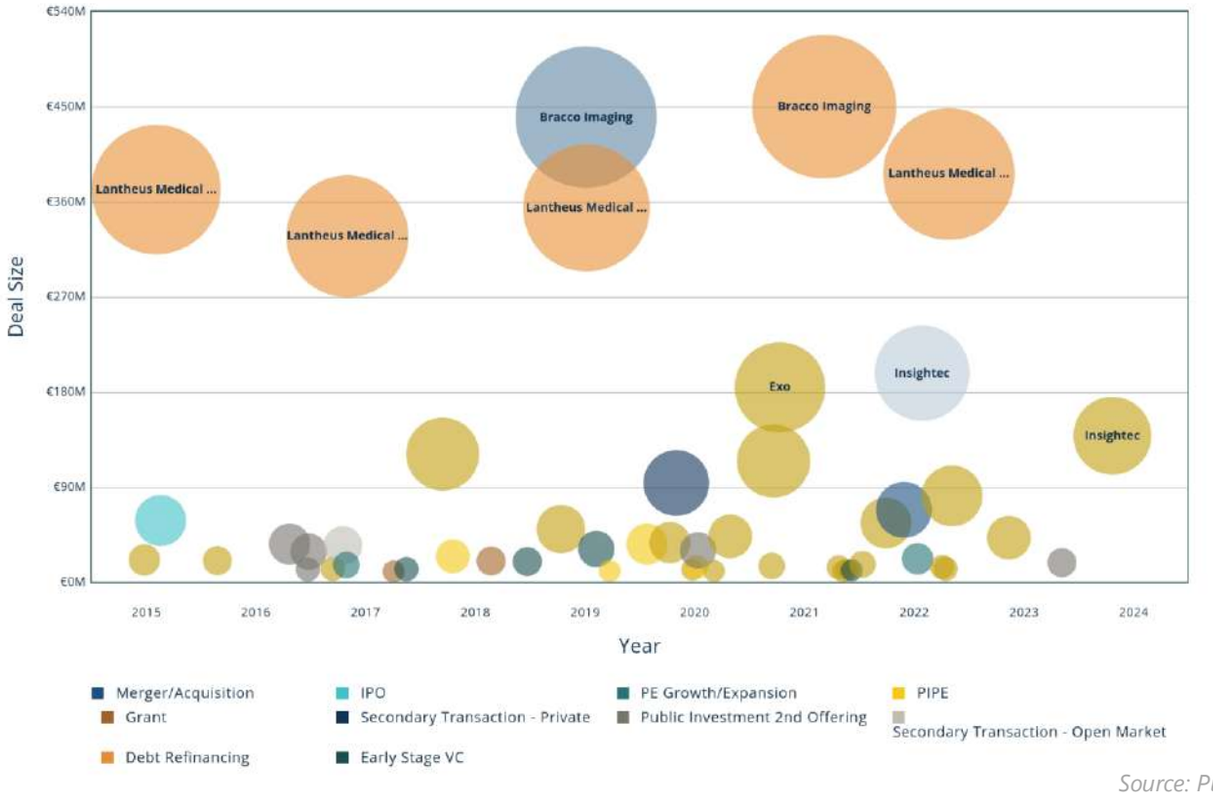
Pricing of drug delivery platforms is 10x higher than HIFU device makers

Reimbursement policies in the US have been evolving positively, including HIFU therapies in Medicare and Medicaid services, and via selected private payers as cost-effectiveness is validated. Coverage has increased over the past couple of years from USD 8.6k in 2022 to USD 13k. Nonetheless, the major potential for capitalising on FUS solutions lies ahead, as innovations that function as drugs will be priced accordingly. We can anticipate proprietary drug-delivery platforms to fall into the same category and be priced as co-drugs within the same range as other commercial drugs used to treat the disease in question. We therefore anticipate a much larger pricing opportunity. For example, EXACT Therapeutics could see its ACT Therapy for pancreatic cancer set a list price of USD 100-200k, 10x higher than any other FUS hardware-based solution.

Largest financing rounds led by MB companies

As we mapped the sector, we identified **Bracco Imaging** (private, Italian) and **Lantheus Medical Imaging** (public, US) as the two major providers of microbubbles used in ultrasound, which also stand out with the largest debt refinancing deals. Given the early stage of Low-Medium Intensity Focused Ultrasound players, both across the US and EU, the smaller round sizes are not surprising. Deals related to **Insightec** (private, Israel) mark it out out as the most established company in HIFU.

Figure 21 - FUS deal landscape



Source: Pitchbook

Europe to bring pivotal technologies in drug delivery, oncology and structural heart diseases…

Three European companies have marketed products within HIFU, while the other four are leveraging Low-Medium Intensity Focused Ultrasound and have products that are under clinical development (see Table 3). As we highlighted for non-thermal FUS applications, it is in Europe where we found the most compelling and advanced cases, which we will follow closely and keep on our radar. These are: i) **EXACT Therapeutics**, whose proprietary drug-delivery platform is progressing into phase 2 clinical study in pancreatic cancer; ii) **Carthera**, with ongoing pivotal studies evaluating SonoCloud-9 in GBM; and iii) **Cardiawave**, a unique payer using histotripsy to restore softness in calcified heart valves.

Table 3- Selection of European-based FUS companies

Company name	Ownership	HQ	Device	FUS modeality	Application	Stage	Last deal date	Deal type	Last deal raise (EURm)	Total raised (EURm)
CARTHERA	Private	France	SonoCloud	Mechanical	Opening of BBB for enhanced drug delivery in the brain	Clinical	27/06/2023	Series B	42	82
EYE TECH CARE SOUND GLAUCOMA CARE	Private	France	EyeOP1	Thermal	Glaucoma	Market	16/08/2022	PE	22	69
THERACLION	Public	France	SONOVEIN ECHOPULSE	Thermal	Varicose veins, thyroid nodules and breast fibroadenoma	Market	11/06/2018	PIPE	4	35
OxSonics	Private	UK	SonoTran	Mechanical	Drug-agnostic platform to enhance and monitor drug delivery	Clinical	01/07/2020	Series B2	12	25
CARDIAWAVE	Private	France	VALVOSOFT	Mechanical	Heart valve diseases	Pivotal	13/09/2022	Later Stage VC	2	21
EXACT Tx	Public	Norway	ACT Therapy	Mechanical	Proprietary MB to enhance drug delivery across tumour barriers	Clinical	01/12/2023	PIPE	2	16
edap tms	Public	France	Ablatherm Focal One	Thermal	Prostate cancer	Market	01/08/1997	IPO	33	49

Source: BG IRIS, Pitchbook

…while the first FDA-approved nonthermal FUS tech came from the US

HistoSonics, Sonothera and **Cordance Medical** were presented in this paper as providing differentiated technologies within their field of expertise. Other nonthermal US FUS companies include Apheus Medical, Cerevast and Sonovascular.

Table 4- Selection of US-based FUS companies

Company name	Ownership	Device	FUS modeality	Application	Stage	Last deal date	Deal type	Last deal raise (EURm)	Total raised (EURm)
HISTOSONICS	Private	Edison Platform	Mechanical	Histotripsy in liver cancer	Market	13/12/2022	Later Stage VC	82	194
PROFOUND	Public	TULSA PRO	Thermal	Prostate cancer	Market	16/01/2024	PIPE	3	169
SONOTHERA	Private	-	Mechanical	Nonviral gene delivery platfomr	Clinical	29/04/2022	Later Stage VC	56	56
Alpheusmedical	Private	-	Mechanical	BBB opening to address GBM	Clinical	09/11/2022	Later Stage VC	14	29
sonablate HIFU	Private	Sonablate HIFU	Thermal	Prostate cancer	Market	03/08/2023	PE	Unkown	24
CEREVAST	Private	-	Mechanical	Ischemic stroke, Retinal vein occlusions	Clinical	01/07/2021	Secondary Transaction - Private	Unkown	18
sonovascular	Private	SonoThrombectomy	Mechanical	Arterial and venous thrombosis.	Clinical	05/01/2024	Later Stage VC	1	7
Cordance MEDICAL	Private	NeuroAccess	Mechanical	BBB opening to address GBM, liquid biopsy	Clinical	01/12/2023	Accelerator	Unkown	5

Source: BG IRIS, Pitchbook

Strategic R&D partnerships validate the industry's potential

In late 2023, **GE Healthcare** and **Novo Nordisk** entered into a partnership to advance peripheral focused ultrasound (PFUS) therapy, a non-invasive, non-pharmacological treatment **for chronic diseases such as type 2 diabetes and obesity**. Pre-clinical and early clinical data suggest that PFUS can regulate metabolic functions and potentially normalise blood glucose levels through personalised ultrasound stimulation of nerve pathways. This collaboration leverages GE HealthCare's ultrasound technology expertise and Novo Nordisk's experience in metabolic disease management to develop innovative solutions for improving patient care amidst the growing global burden of diabetes and obesity.

Quiet M&A for now, but big MedTech is following the space closely

While the FUS market has not triggered an M&A deal to date due to its early stage, we would not be surprised to see deals as the sector matures. We already see signs of support from the established MedTech imaging companies acting as lead investors. For instance, **Jonhson and Johnson's innovations** led HistoSonic's last financing round of EUR 82m in December 2022, and SonoThera's EUR 56m capital raise in April 2022. Additionally, EXACT Therapeutics **is a spin-off from GE Healthcare**, which is also one of the major providers of Dx microbubbles.

Also, a clear biotech angle

As innovations in the context of drug delivery revolve around proprietary microbubbles rather than pure MedTech hardware, we could expect M&A to emerge from the biotech angle. Any drug developers whose asset efficiency could benefit from enhanced delivery could be interested in FUS MB solutions.

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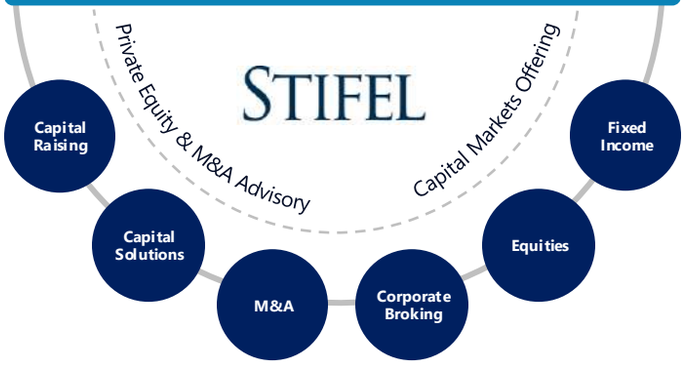

CORE SECTOR EXPERTISE


Diversified Industries


Healthcare


Natural Resources

FIG


Infrastructures


Real Estate


Technology

Note: (1) As at 02 February 2025; (2) as of 31 December 2024

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