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Magnetic Resonance Guided Focused Ultrasound: A New Technology for Clinical Neurosciences

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Introduction

Diseases of the central nervous system (CNS) account for more hospitalizations and a greater need for long-term care than most other clinical areas. Most currently available therapeutic interventions are suboptimal. Surgery, radiation therapy, and drug delivery all have significant limitations, therefore, completely new approaches and technologies are desperately needed.

Over the past two decades, we and others have developed the fundamentals of transcranial magnetic resonance imaging-guided focused ultrasound (TcMRgFUS), a non-invasive technology that, according to those who are familiar with it, will profoundly impact all aspects of the clinical neurosciences (1–7). TcMRgFUS is a disruptive technology that can improve upon or replace existing treatments and enable therapies that are not possible today. It is a radical departure from current treatment methods and involves expertise from multiple disciplines. While the full potential that focused ultrasound (FUS) can have for disorders of the CNS is not widely known, the transformational process has already begun.

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As we describe in this chapter, FUS has the ability to precisely focus acoustic energy to anatomically and functionally targeted locations in the brain and non-invasively induce a broad range of bioeffects that can be utilized to develop new diagnostic and therapeutic methods. Despite this great promise, this new enabling technology has several critical hurdles to overcome before widespread clinical translation is possible; a large-scale concentrated multidisciplinary effort is necessary. Currently a diverse team of physicists, neuroscientists, engineers, and clinicians are working to advance FUS in clinical applications with the greatest impact. This review is based upon innovations made by our group and others that have demonstrated the promise of TcMRgFUS. There are only a few prior examples of any other technology that has the same disruptive and transformative potential in any other field of medicine. If translated into every day clinical practice, this enabling technology will change all aspects of clinical neuroscience.

FUS is uniquely capable of producing changes that can be used for the treatment of a potentially extensive range of CNS diseases and disorders. It is a completely non-invasive, targeted, and repeatable method that can be integrated with MRI to enable the necessary precise anatomical and functional guidance and control of energy deposition (8,9). MRgFUS has been applied to treat both benign and malignant tumors like uterine fibroids, breast tumors, prostate and liver cancer, and bone metastases (8–10). The capabilities of FUS not only include the ability to non-invasively ablate tissue volumes (potentially replacing neurosurgery and radiosurgery), but also to deliver drugs to targeted brain regions through a temporary disruption of the blood-brain-barrier (BBB)(11). This FUS-mediated method can revolutionize both neurooncology and neuropharmacology. In addition, FUS can reversibly modulate neuronal function (providing a tool that can be used both in diagnosis and treatment in basic or clinical neuroscience)(12–14).

In recent years, with the development of a commercial TcMRgFUS device that is capable of focusing ultrasound through the human skull, the feasibility of the technology was proven in humans in brain tumor ablation and functional neurosurgical applications (7, 15). Also through a large number of pre-clinical studies that have been published recently, it has become clear that this technique has matured and is ready to be translated into clinical practice. However, this translation will be difficult as, to most, the therapeutic use of ultrasound in the brain is a radical concept. Therefore, significant work is needed to prove that FUS can be applied safely. Indeed, progress has been slow with the feasibility of TcMRgFUS thermal ablation in humans only being reported within the past few years (7, 15).

History of Brain FUS

FUS has been investigated for more than 50 years, primarily for non-invasive ablation in the brain as a potential alternative to surgical resection, functional neurosurgery and radiosurgery (16–21). The enormous benefits of applying FUS as a non-invasive method for treating brain tumors, epilepsy, and movement disorders have been understood for many years, but the need for a craniotomy and the absence of imaging technologies delayed its development. Until recently, clinical tests of the method have required the removal of a section of the skull (22) to allow for ultrasound propagation into the brain due to high

ultrasound absorption and heating of the skull bone and beam phase aberration caused by the skull's irregular shape and thickness and its large acoustic impedance.

The acoustic energy deposited in the focal region can be utilized in a surprisingly large number of ways and has fascinated neuroscientists for more than 60 years (16–21,23). In the last 10–15 years, significant technological developments made by our group and others have made the use of FUS in the brain a reality. The creation of devices that can safely and precisely focus high intensity ultrasound beams through the intact human skull (2,3), and the integration of these devices to high-field MRI (4–6) have made it realistic to expect that technology will reach its potential in multiple clinical applications. Initial human trials with these devices are ongoing (7, 15), and the research community investment in focused ultrasound technology is growing exponentially. While MRgFUS technology has great potential for targets throughout the body, its greatest potential in our view is in the brain because of the lack of invasiveness. TcMRgFUS can overcome significant limitations of current therapies because it can spare normal structures adjacent to the therapeutic target. The potential of FUS for non-invasive brain tumor treatment and functional neurosurgery was recognized already in the 1950's and several investigators tried to develop a clinically applicable device (18–22,24–31). However, several technical problems have prevented the use of FUS in humans. Among those problems are the issues of penetration of the acoustic beam through the intact skull and localization of both the target and the focus. The need for large craniotomies to create sufficient acoustic windows and the lack of tumor definition and temperature sensitive imaging were the main reasons that brain FUS was not developed.

The solutions for these problems surfaced in the early 1990s. MRI was integrated with FUS and used for target definition and for the control of energy deposition by MRI-based temperature sensitive imaging (32,33). To transfer a sufficient amount of acoustic energy a large number of phased array transducer elements were applied, and the difficulty of focusing through the irregular skull was resolved by using x-ray computed tomography (CT) to measure skull thickness at each transducer elements and to correct phase aberrations (2,4–6, 34,35). As a result, the world first TcMRgFUS system (ExAblate 2000) was developed by Insightec (Haifa, Israel). Currently, an updated 1000 element version (ExAblate 4000) at 650 kHz is used for initial human clinical trials for brain tumors and functional neurosurgical applications at multiple academic sites (Fig.1.).

The TcMRgFUS systems reduce skull heating through active cooling of the scalp and have a transducer design with a large aperture to distribute the ultrasound energy over a large skull region. Further, using a complex phased array transducer design, they correct for phase aberrations. When combined with methods that use acoustic simulation based on CT scans of the skull bone to determine the phase and amplitude corrections for the phased array and MR temperature imaging to monitor the heating, a completely non-invasive alternative to surgical resection in the brain becomes possible.

The potential applications of TcMRgFUS are wide-ranging (20). The ExAblate Neuro system is under evaluation for clinical safety and efficacy in functional neurosurgery (15) and tumor ablation (7). In these early implementations, the imaging of the thermal focus and the safety of skull heating were demonstrated.

In functional neurosurgical trials up to date more than 50 patients have been treated for movement disorders (essential tremor and Parkinson's disease) and more than 20 for neuropathic pain. The Essential Tremor Phase I trial was completed. Multi-site pivotal studies are under development. It can be concluded that MRI-based temperature monitoring provides accurate targeting and safe energy deposition during thalamotomies. Other CNS diseases that can be treated with TcMRgFUS in the future are: epilepsy, obsessive compulsive diseases (OCD), and trigeminal neuralgia.

The major issues that have hindered the use of FUS in the brain in the past have been solved, and there is no longer any question that the technique can be delivered through the intact skull in humans. With these hurdles surpassed, we should dedicate our efforts to bringing novel, innovative FUS therapies beyond thermal ablation to the clinical fields of neuroscience. These novel non-thermal techniques, achieved through the combination of FUS and injections of pre-formed microbubbles, have the potential to greatly expand the abilities of FUS in the brain. While significant work has already been done by our team and numerous other research groups, significant issues remain to be resolved before they can be translated to the clinical practice.

TcMRgFUS of Brain Tumors

Despite progress in drug development, radiation therapy, and radiosurgery, the standard of care for many patients with CNS tumors remains complete or incomplete (debulking) surgical resection, which is an invasive and risky procedure. Despite advances in therapy malignant brain tumors remain an extraordinary challenge. Due to the inherent risks associated with surgical resection and radiation therapy, combined with the aggressiveness of many CNS tumors and the difficulties of drug delivery in the brain, the prognosis for patients with many types of CNS tumors remains grim. New and less invasive alternatives are desperately needed. Technologies that can precisely ablate tumors while sparing surrounding critical structures would be a huge benefit to brain tumor patients. Thermal ablation has been pursued as a less invasive alternative to surgery for tumor therapy in several targets (36, 37) including the brain (38–40). FUS has been investigated for non-invasive ablation in the brain as a potential alternative to surgical resection and radiosurgery (20,21,41–43). Until recently, clinical tests of the method required removing a section of the skull for ultrasound propagation into the brain (22, 42–47), given that there is high ultrasound absorption and heating of the skull bone and beam aberration caused by the skull's irregular shape and large acoustic impedance.

In the past decade, FUS thermal ablation systems have been developed that overcome these obstacles produced by the skull (48, 49, 50). As mentioned, they reduce skull heating through active cooling of the scalp and a transducer design with a large aperture to distribute the ultrasound energy over a large skull region, and, importantly, they correct for beam aberrations using a phased array transducer design. When combined with methods that use acoustic simulation based on CT scans of the skull bone to determine the phase and amplitude corrections for the phased array (2,3) and MR-based temperature imaging to monitor the heating (51–53), a completely non-invasive alternative to surgical resection in the brain becomes possible. These systems have been tested in animals (4, 54) and in initial

human trials (15, 55). Such systems may also be useful for ultrasound-based targeted drug delivery methods in the brain (11) and for the treatment of stroke (56)

TcMRgFUS offers clear, unambiguous advantages over other current treatment modalities (surgery, radiation therapy, and probe-delivered thermal ablations like interstitial laser therapy), as it is non-invasive (i.e., incisionless, scarless, bloodless) and does not involve ionizing radiation. Therefore, complications such as bleeding and infection are minimized, and because the MRI-guided targeting collateral damage to non-targeted tissue is almost nonexistent. The goal of ideal brain tumor surgery is complete removal of the entire tumor volume of the target lesion with functional and structural preservation of the surrounding tissue, including sparing of the tissue in the surgical path. An invasive or even minimally invasive surgical procedure is only an approximation to the “ideal surgery”. The ideal therapeutic modality, TcMRgFUS, is non-invasive and targeted at the point of acoustic convergence, thereby sparing the overlying tissue and it deposits sufficient thermal energy to ablate even deep-seated tumors.

Certain primary malignant brain tumors, particularly gliomas, invade and infiltrate the normal brain and, therefore, they cannot be completely removed or ablated without associated injury of normal tissue and related functional damage. In most of these patients, tumor debulking by surgery to decrease tumor volume can be considered a satisfactory outcome. Benign tumors and most metastases, on the other hand, demonstrate more confined and often well-defined borders, in which case complete destruction of tumor volume would be deemed adequate treatment. However, whether in gross total or total resection, MRgFUS unmistakably maintains anatomic and functional preservation of the surrounding brain parenchyma. Furthermore, in the case of debulking surgery, specifically in glioblastoma, where recurrence will invariably occur, FUS allows for unlimited retreatment sessions, an option not present in surgery or radiation therapy. The ability to repeat unlimited treatment sessions coupled with the presence of real-time intraprocedural feedback (closed-loop control of the deposited thermal dose) provides a personalized treatment, especially when confronted with geometrically asymmetric or noncircular target lesions that are difficult to cover with probe delivered ablations. Secondary tumor formation, caused by radiosurgery and radiotherapy, does not occur with FUS therapy. Furthermore, because the thermal gradients of FUS are much narrower than the dose curves in radiotherapy, FUS is more precise and causes less thermal damage to adjacent tissues.

Brain surgeries at the skull base, in particular, even for benign tumors, are particularly difficult due to their location and proximity to critical nerve and vascular structures (57). Although skull base surgical approaches are used for vascular disease, congenital anomalies, and some non-neoplastic bony disorders, difficulties for surgical management remain and are related to the presence of critical structures: cranial nerves, blood vessels, and the brainstem. Access is also limited by bony structures and the presence of air-containing paranasal sinuses. Radiosurgery can also be challenging to use without damaging these critical structures. While extraordinary advances have been made in neurosurgical techniques that permit better surgical access to these challenging regions in the brain, surgery near the skull base has remained a traumatic, time consuming procedure that poses significant risk to patients, who are often poor candidates for surgery. Surgical resection of

recurrence can also be a challenge. In recent years, the field of skull base surgery has been revolutionized by multidisciplinary improvements in anesthetic and surgical techniques. The development of brain exposing osteotomies, neuro-endoscopic surgery, infection prevention methods (e.g., galeal, frontalis, and myofascial flaps), and improved techniques for reconstruction allow surgeons to perform biopsies and resections on many skull base masses. In addition, radiosurgery with Gamma Knife or a Linear Accelerator (LINAC) has become a highly useful tool in treating pathologic conditions at the skull base. As expertise with surgical approaches to the skull base has grown, the optimal application of these methods in combination with adjuvant therapies has become the focus of skull base neurosurgery, which is invasive even using the best surgical approaches. Nevertheless, many skull-base tumors, even benign ones are not operable because the danger of vision loss or of other essential functions because of cranial nerve injury.

TcMRgFUS provides alternatives to surgical resection and radiosurgery that can remotely target tissue volumes in the brain, even at the skull base, while sparing the surrounding tissues. As we describe below, FUS has the potential to provide new “surgical” options for patients who fail after surgery or radiosurgery. Ultimately, with enough research to prove its safety and efficacy, it may ultimately replace them. The technology of TcMRgFUS can greatly extend FUS brain surgery, making it possible throughout the brain.

The effects of FUS can be enhanced by combining sonications with microbubble agents. These agents, which are available as ultrasound imaging contrast agents, consist of semi-rigid lipid or albumin shells that encapsulate a gas, typically a perfluorocarbon. They range in size from about 1–10 μm and are constrained to the vasculature. The presence of the preformed microbubbles that make up the contrast agent circulating in the vasculature concentrates the ultrasound effects to the microvasculature and greatly reduces the FUS exposure levels needed to produce bioeffects. Thus, with these microbubbles we can apply FUS transcranially without significant skull heating or distortion of the ultrasound beam. When microbubbles interact with an ultrasound beam, a range of biological effects has been observed. Depending on their size, the bubbles can oscillate within the ultrasound field, growing in size via rectified diffusion. At high enough acoustic pressures, they can collapse during the positive pressure cycle, a phenomena known as inertial cavitation, producing shock waves and high-velocity jets (58), free radicals(59) and high local temperatures (60, 61). In addition, the medium surrounding the bubbles undergoes acoustic streaming (62) which may be associated with large shear stresses. Further, a radiation force on the bubbles is produced along the direction of the ultrasound beam (58). The preformed microbubbles used in ultrasound contrast agents presumably can exhibit these behaviors, either with their shells intact or after being broken apart by the ultrasound beam and their gas contents released.

A current limitation of TcMRgFUS is that thermal ablation is restricted to brain targets that are distant from the skull bone. If the focal point is placed in peripheral regions, the incidence angle between large portions of the skull bone and ultrasound wave front becomes more oblique. As this angle increases, less of the ultrasound beam penetrates the skull, and at extreme angles, the beam is totally reflected. As a result, fewer elements in the array can be effectively utilized when peripheral regions are targeted, increasing the peak energy

density and the heating on the skull surface. Shear mode conversion also increases as this angle increases, further increasing the heating due to the higher absorption coefficient of the shear mode. This limitation was evident in analysis of MR temperature measurements in the focal region and on the brain surface in the first patient treatments with a TcMRgFUS system (55). Placing the focal point near the skull base adds an additional challenge, as the beam in the far-field (i.e. beyond the focal point) will heat the bone and could damage nearby brain, nerve, and vascular structures. Large myelinated nerves may be at particular risk due to their lower vascularity and perfusion that prevents the heat from being drawn away. To target peripheral areas and targets near the skull base with TcMRgFUS, new methods are needed.

One way to increase the focal heating without increasing the time-averaged acoustic power deposition (which determines the degree of skull heating) is to use microbubble-enhanced heating (63,64). By employing US bursts with peak pressure amplitudes above the cavitation threshold, microbubbles are generated from gas nuclei within fluid in the tissue. These microbubbles can locally enhance the heating in the focal zone through viscous heating, absorption of bubble acoustic emission and other factors (63). If the ultrasound bursts are delivered with a low duty cycle, the time averaged intensity on the skull can potentially be largely reduced. While this approach can expand the targetable areas for TcMRgFUS, it would not permit ablation of targets directly adjacent to the skull bone. To target such areas, a more radical decrease in the time averaged acoustic power will be necessary. A way to achieve this reduction is to combine FUS with an intravenously injected microbubble-based ultrasound contrast agent.

At slightly higher exposure levels, the microbubbles collapse violently, leading to vascular destruction and tissue death in the focal region. This method for “non-thermal” ablation, which can be applied without overheating the skull, can greatly expand the areas of the brain that can be targeted compared to thermal ablation, providing a non-invasive alternative to surgery and radiosurgery. The current standard of care for many primary brain tumors and brain metastases includes radiation therapy. While it is effective and improves outcomes, its effectiveness is limited. Most importantly, it cannot be repeated in the case of recurrence, which occurs frequently, and at which time a patient’s options are limited or nonexistent. In radiation therapy and radiosurgery (Gamma Knife, LINAC, proton beam, etc.) the radiation dose is statistically set based on accumulated prior experience, and, because of their toxic cumulative effects, lend themselves to only a single treatment session (irrelevant of the treatment success). On the other hand, FUS, is nontoxic, allowing for unlimited treatments in a single session and unlimited repeated sessions over a period of time, which is a feature of particular importance when a tumor recurs. In addition, unlike radiosurgery, FUS effects can be performed under image guidance with high-field MRI, which provides outstanding anatomic definition of the target site, real-time guidance and monitoring during therapy, and immediate post-treatment confirmation of the treatment effects. For FUS thermal ablation, magnetic resonance thermometry (52, 33,34) in FUS therapy permits accurate real-time non-invasive intraprocedural monitoring.

There is a need to develop methods to provide similar feedback during microbubble-enhanced FUS applications. We also need to evaluate whether radiation-induced changes to

the tissue have an effect on the safety and efficacy of these FUS/microbubble techniques. Radiation induces changes to the vasculature, which may make it more or less sensitive to the mechanical effects induced by FUS and microbubbles. Other changes to the tissue may change its response to the therapy, such as altering drug penetration after BBB disruption. Before patients who have had radiation are treated with FUS and microbubbles, we need to establish that it can be done safely and understand how radiation can change the outcome of the therapy. Combining microbubble-enhanced FUS with high-resolution MRI offers a means to non-invasively and precisely target tumors or other regions anywhere in the brain, including the skull base. FUS produces immediate ablation. It is repeatable, and it can be applied without general anesthesia. No other technology is available that can achieve this result. We and others have spent the last decade developing FUS and MRI technologies that have allowed clinical trials of thermal ablation (7, 15). In contrast, research combining FUS with microbubbles for ablation in the brain is only just beginning, and substantial work is needed to apply it reliably in a controlled manner and to understand and optimize the ablation process.

Recent work has demonstrated that the method is ready for such intense testing and has the potential to have a large impact as a replacement for surgery and radiosurgery. We tested the ability to ablate targets at the skull base in rats next to the optic chiasm and optic tract without impacting nerve function. Before FUS, MRI compatible electrodes were placed bilaterally on the dura above the primary visual cortex, and visual evoked potential (VEP) measurements were acquired. These measurements were repeated weekly after a sonication on or adjacent to the optic tract or chiasm to determine whether visual function was intact. We found that this was possible and that histology showed that the fibers in the tract were mostly intact, even when the lesion was directly adjacent to it, and no significant changes were observed in the VEP measurements.

We have also evaluated the feasibility of ablating brain structures adjacent to the optic nerve in nonhuman primates with the low-frequency TcMRgFUS system. In rhesus macaques we found that discrete lesions were produced at the targets that were consistent with our prior experience in rats. Based on histology and observation after the monkeys recovered from anesthesia, the optic tract appeared to be only minimally effected. These results are highly encouraging and demonstrate that non-invasive ablation can be achieved with this TcMRgFUS system even at the skull base without overheating the bone and damaging surrounding structures.

This result would not be possible with any existing radiosurgery technology including proton beam therapy. Using this method there is a sharp demarcation between treated and untreated areas. The TcMRgFUS system not only has a great targeting accuracy, but it also can be monitored real-time and with subthreshold energy levels that cause no irreversible tissue damage. The lesion location can be identified before irreversible lesions are made. To get this method to patients, we have developed a plan to optimize the exposures, monitor the effect in real-time, and to test the safety of the method in nonhuman primates.

Targeted Drug Delivery

Most systemically administered therapeutic agents are not effective in the CNS because they are blocked by the BBB. The BBB restricts the passage of substances except for small (molecular weight < ~400 Da), hydrophobic molecules, preventing most small-molecule drugs and essentially all large-molecule drugs from reaching the brain interstitial space (65). It is the primary hurdle to the development and use of drugs in the CNS. As many as one-third of the population is expected to experience a CNS disorder in their lifetime, but the global pharmaceutical market for CNS-related drugs would have to increase by a factor of five to equal that for cardiovascular disease. Most methods that have been tested to circumvent the BBB are invasive, non-targeted, or require the expense of developing new drug carriers that utilize endogenous transport mechanisms (65). Because of the BBB, most chemotherapies have not been very effective treatments for malignant brain tumors. While the vessels in most brain tumors do not have a fully intact BBB and can be permeable, infiltrating cancer cells and small metastatic seeds are disseminated in the normal brain, where the normal brain blood vessels and the BBB prevent drug extravasation (66). Furthermore, it is known that tumor vasculature permeability is heterogeneous and that there are additional barriers to drug delivery, such as increased interstitial pressures (67) and efflux pumps (68,69). Major efforts have thus been undertaken to develop pharmaceuticals that circumvent the BBB, such as designing more lipid-soluble drugs, designing water-soluble drugs with high affinities for natural carriers at the BBB, or through the use of vectors such as amino acids and peptide carriers (70–72). Others have diffusely and reversibly disrupted the BBB by introducing a catheter into an arterial branch within the brain and applying an infusion of hyperosmotic solution or other substances (73). The only current method to deliver drugs to selected regions of the brain is directly to inject agents or to use implanted delivery systems (74). A method to disrupt the BBB non-invasively and reversibly at targeted locations would have a major impact on clinical neuroscience. Indeed, the National Institutes of Health Brain Tumor Progress Review Group recently recognized the need for such targeted drug delivery (76). Unfortunately, most of the methods that have been tested to circumvent the BBB are invasive, non-targeted, or require the expense of developing new drug carriers that utilize endogenous transport mechanisms.

The combination of FUS with circulating microbubbles, which directs the acoustic effects to the vasculature and reduces the energy needed to produce bio-effects, can greatly expand brain applications of FUS beyond thermal ablation. At low exposure levels, the combination of FUS and microbubbles induces a temporary permeabilization of the blood vessels in the brain and in brain tumors, leading to a targeted way to get drugs past the BBB. The combination of FUS and circulating microbubble agents has the potential to revolutionize drug delivery to the brain. This technology enables the crossing of drugs across the BBB, to deliver drugs to a preferred target, and to do it non-invasively so it can be readily repeated to match a patient's drug schedule. Today, even when drugs are applied that have maximal efficiency preferentially at the target tissue, systemic toxicity can still occur and limit the dose. With MRgFUS, preferred targeting can occur even with systemic administration because the BBB is disrupted only in the desired location. Ultimately, this can be extended because the drugs can be designed for FUS-triggered release through encapsulation in gas-

containing bubbles, liposomes, nanoparticles or other carriers before being administered systemically.

Microbubble-induced opening of the BBB is transient and reversible. No permanent histological damage is seen, and the function of BBB is preserved after a few hours. The increased permeability for larger molecules is most likely explained by the acoustic-mechanical effect of US on the tight junctions (11, 76–84). Transfer of various size molecules has been demonstrated after FUS- induced BBB disruption. That included antibodies (85), chemotherapies like Herceptin (86) and Doxorubicin (87–89) and DNA (90).

The increased BBB permeability and the improved delivery of chemotherapies were tested in animal experimental tumor models. Tumor growth and survival rates were monitored via MRI for seven weeks after sonication. HER 2/neu-positive breast cancer metastasis models were treated with trastuzumab and, in almost half of the animals, the tumor appeared to be completely resolved in MRI, an outcome which was not observed in control groups (91). Similar results were seen with Herceptin treatments. 9L gliosarcoma of rats was treated with liposomal doxorubicin. Post-treatment MRI showed that following FUS-mediated BBB opening Doxorubicin reduced tumor growth compared with controls without FUS treatment (88). There was a modest but significant increase in median survival time after a single FUS +DOX treatment, whereas neither DOX nor FUS had any significant impact on survival on its own. These results suggest that combined ultrasound-mediated BBB disruption may significantly increase the antineoplastic efficacy of liposomal doxorubicin in the brain.

The use of FUS to temporarily disrupt the BBB overcomes the greatest single hurdle to the development of therapies for CNS disorders. Being able to modify this barrier and allow drugs to reach the brain and to be able to do it only in the locations where the drugs are needed will revolutionize drug therapies in the brain. It is important that we can do this safely and in a controlled way.

The presence of the BBB is the primary hurdle to the development and use of drugs in the CNS. As many as one-third of the population is expected to experience a CNS disorder in their lifetime, but the global pharmaceutical market for CNS-related drugs would have to increase by a factor of five to equal that for cardiovascular disease. The opportunity that FUS technology presents is to overcome these restrictions. Enabling in the brain the full arsenal of drugs and removing limitations that currently hinder drug development for CNS disease would obviously lead to long-term improvements and growth in research, enterprise, public health, and health care delivery.

Whereas most brain disorders may benefit from this approach, the first obvious target for this technology would be to deliver anticancer drugs to brain tumors and the surrounding brain that may be infiltrated. While primary brain tumors may be good targets for this technology, a more immediate target could be brain metastases from non-CNS tumors. We expect that brain metastases will be the best application for initial clinical tests as brain tumor patients lack treatment options, and there are existing approved agents that are known to be effective with extracranial disease.

We recently completed in preparation for clinical work a safety study of the technique in nonhuman primates using a commercially available TcMRgFUS system (92). We have tested this device in 40 sessions in 10 rhesus macaques. After sonicating more than 200 discrete loci or larger volumes in the brain, we have found that the BBB disruption can be achieved safely with no evidence for either histological or functional damage. This result was true even when the same brain target was sonicated repeatedly five or more times over several weeks.

The ability of FUS-induced oscillations of circulating microbubbles to permeabilize vascular barriers such as the BBB holds great promise for non-invasive targeted drug delivery. A major issue has been a lack of control over the procedure to ensure both safe and effective treatment. Passively-recorded acoustic emissions may achieve this control. An acoustic emissions monitoring system was constructed and integrated into a clinical tMRgFUS (93) to control focused ultrasound-induced BBB disruption. We found that this monitoring system provides signatures that can predict both BBB disruption and the small vessel damage that occurs with overexposure. Overall, this study demonstrated that the method can be applied safely, reliably, and in a controlled manner using a commercial TcMRgFUS system that is already available for patient use.

Such promising results along with the growing body of literature on this technique demonstrate its safety and effectiveness and are supportive of its translating to patients.

Neuromodulation

In the past decade, neuroscience has been revolutionized by the ability to non-invasively map brain function, and to a lesser extent, to modulate regional brain activity in a controlled manner. Applications of neuromodulation range from functional testing to the treatment of diverse neurologic or neuropsychiatric disorders. Subdural and epidural cortical stimulation as well as deep brain stimulation (DBS) are finding increasing acceptance in neurotherapeutics. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) offer non-invasive alternatives but lack spatial specificity and have limited depth of penetration. The ability of these technologies to image and modulate neuronal function has led to an explosion of studies that are providing a deeper understanding of brain function and potential therapies for CNS disorders.

We think that such abilities would be just the tip of the iceberg of what can be achieved with TcMRgFUS, which offers capabilities that are not possible with any other technology. It has been known for decades that FUS can stimulate the brain (12,13,94) and can block nerve conduction (95). FUS can modulate brain function by itself, which is a completely new way to diagnose and treat a range of CNS disorders and to study brain function. We need a deeper understanding of how we can use FUS to modulate brain function that can be translated to clinical tests. Transient modulation of brain function using image-guided and anatomically-targeted FUS would enable the investigation of functional connectivity between brain regions and will eventually lead to a better understanding of localized brain functions. It is anticipated that the use of this technology will have an impact on brain

research and may offer novel therapeutic interventions in various neurological conditions and psychiatric disorders.

The mechanism by which FUS achieves neuromodulation is not known, but it is thought that it could be related to transient changes in cell membrane permeability (14). With devices that can precisely focus an ultrasound beam through the intact human skull, we can non-invasively target small volumes deep in the brain, greatly improving upon the capabilities of TMS. We can combine FUS-induced neuromodulation with simultaneous functional imaging, providing real-time evaluation of the effects of suppression and stimulation of neural circuits. These technologies can be combined for complex experimental designs involving different stimuli, tasks, and mapping of functional activity throughout the brain.

In rabbits we demonstrated that the pulsed application of low-intensity FUS bursts (i.e., lower than the intensity approved for diagnostic ultrasound imaging) can modulate neural tissue excitability through nonthermal mechanisms (14). We have also reduced chemically-induced epileptic states in rats (96) and have demonstrated that FUS can modulate the extracellular level of dopamine and serotonin when applied to the rat thalamus.

In addition to the potential of using FUS alone for neuromodulation, we can also use FUS-induced BBB disruption to deliver neuroactive agents to targeted specific locations in the brain, which is an ability that opens exciting new opportunities for neuromodulation. Translating this technology to the clinic will be more challenging than the other FUS applications that aim to provide new and less invasive treatments to desperately sick patients with brain tumors. While it has potential application neurosurgical planning, especially for functional neurosurgery, we think its main potential lies in other areas such as those in which TMS or other methods for stimulation are used (movement and psychiatric disorders, for example) and in healthy subjects for neuroscience research.

If we establish the safety of the method and work out its technical challenges, we will provide an unparalleled research opportunity for the study of brain function non-invasively. Being able to non-invasively and repeatedly modulate the levels of neuroactive agents opens the door to new investigations that exploit specific molecular pathways. In addition to neurotransmitters, one can envision targeting the delivery of other substances such as neurosteroids or neuropeptides (perhaps encapsulated to allow for systemic application) that induce specific effects on different neuronal populations. Being able to do such experiments in alert animals with simultaneous fMRI would be a powerful tool to improve our understanding of brain function and potentially to develop new methods to diagnose and treat disorders of the CNS.

Conclusion

TcMGFUS is an old idea but a new technology that may change the entire clinical field of the neurosciences. In neurosurgery it provides an excisionless, scarless, and non-invasive way to treat malignant and benign brain tumors and produce accurate lesions for functional neurosurgical applications. It eventually can replace most of the ionizing radiation-based radiosurgeries. TcMRgFUS has no cumulative effect, and it is applicable for repeatable

treatments, controlled by real-time dosimetry, and capable of immediate tissue destruction. Most importantly, it has extremely accurate targeting and constant monitoring. It is potentially more precise than proton beam therapy and definitely more cost effective. Neurooncology may be the most promising area of future TcMRgFUS applications. It can deliver targeted chemotherapy through open BBB using drugs of any size, therefore, it most likely will change the entire field of neuropharmacology and will have a profound effect on the pharmacology industry. It can be applied to gene therapy and stem cell-based therapy. TcMRgFUS can be used for the treatment of both thrombotic and hemorrhagic stroke. Finally, neuromodulation is an exciting new application that can replace TMS and other modalities, apply neurotransmitters in a targeted way, and localize epileptic foci. The treatments possible with TcMRgFUS, applied alone or in combination, can completely change current clinical practice and open up entirely new directions in the treatment of CNS diseases. While the investigation of therapeutic applications of FUS in brain is not new, clinical translation of this technology has been hampered by its novelty, the relatively large expense needed for clinical translation of new treatments for CNS disease, and the perceived high risks involved in developing and applying new technologies for brain treatments, particularly for non-oncological applications like functional neurosurgery. This need to demonstrate safety creates a dilemma. Early trials are likely going to be done with the sickest of patients; in these trials, patient accrual, industry support, and the ability to improve outcomes may be limited. However, these trials are needed before moving to a broad patient group with which this technology can have its greatest impact. TcMRgFUS is a potentially game-changing revolutionary technology. Pre-clinical data are largely mature, and a clinical device to begin these tests is now available commercially. The need to move FUS forward is substantial and requires resources. Compared to the enormous clinical potential, however, the investment needed to demonstrate that these uses of FUS are possible is small. FUS is a classic “high-risk, high-reward” and truly “transformative” technology for which the reward is uniquely high. This technology has been evaluated for decades, but only now do we have the devices, image guidance, and monitoring or control methods to deliver treatments safely and effectively. So far, all supporting data demonstrate its clinical feasibility and broad applicability.

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- TcMRgFUS has no cumulative effect, and it is applicable for repeatable treatments, controlled by realtime dosimetry, and capable of immediate tissue destruction.
- Most importantly, it has extremely accurate targeting and constant monitoring.
- It is potentially more precise than proton beam therapy and definitely more cost effective.
- Neuro-oncology may be the most promising area of future TcMRgFUS applications.

Fig. 1.
Brain treatment system (Exablate 4000)
Image courtesy InSightec, Ltd., Haifa Israel