Using Ultrasound to Open the Blood-Brain Barrier: New Hope

Lisa O'Mary
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When Graeme F. Woodworth, MD, decided to focus his research efforts on glioblastomas, "everybody thought it was a dead end," the neurosurgeon recalled.

It wasn't an unusual path for him. His first job after undergrad was as a drug discovery chemist at Pfizer.

Graeme F. Woodworth, MD

"Glioblastoma is treated the same way today as it was in 2005," said Woodworth, professor and chair of neurosurgery at the University of Maryland School of Medicine in Baltimore.

That's changing. Numerous multicenter clinical trials have successfully used microbubble-enhanced transcranial focused ultrasound (MB-FUS) to open the blood-brain barrier (BBB) for more than 300 patients across more than 800 sessions. While much

of the groundbreaking work has focused on brain tumors, some early trials have involved patients with Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

And now, Woodworth and colleagues have published a critical part of the roadmap to placing focused ultrasound on the horizon for specialists like neurologists, psychiatrists and — potentially — outpatient technicians to deliver noninvasive treatments or take liquid biopsies across the BBB.

A primary early goal was figuring out how to reliably keep the microbubbles that create the opening from oscillating out of control. What they needed to do was standardize the ultrasound dose.

Precision Sound Measurement

It's been a decade since high-frequency focused ultrasound was first FDA-approved for thermal ablation therapies, with prostate tissue ablation leading the way, and later followed by therapies for essential tremor, Parkinson's disease, epilepsy, and chronic pain.

Now, low-frequency focused ultrasound for brain therapeutics is poised for its last stretch

of research before FDA approval consideration.

Ali Rezai, MD

The parameters discussed in the newly published *Device* paper for reliably opening the BBB address elements such as pulse length, frequency, and acoustic power that "are variable, depending on what company's device you have or what technology you're using. That's why standardization is really important," said co-author Ali Rezai, MD, executive chair of the Rockefeller Neuroscience Institute at West Virginia University in Morgantown, West Virginia, whose team has studied focused ultrasound BBB opening to deliver aducanumab antibodies in patients with Alzheimer's disease.

Focused ultrasound frequencies are so low that they're just out of the range of the best-hearing mammals (bats). The low frequencies are needed to make microbubbles oscillate to create the temporary opening used to deliver drugs or take a liquid biopsy in the brain.

The new paper provides dose parameters for reliable expansion and contraction — called stable cavitation — of the microbubbles. The opening typically lasts 48 hours, Rezai said. Early indications, Woodworth added, are that

the opening starts immediately and then quickly diminishes, meaning during the first few minutes is “when you want your agent to be at peak plasma concentration.”

The new standards rely on acoustic emissions signals. The monitoring method was necessary because high-frequency ultrasound for ablation measured temperature change, but for low frequency, you are monitoring the microbubbles’ motion via sound.

“The ultrasound is 220 kilohertz, so by listening at harmonic frequencies of 220k [physicists have determined how to] hear the bubbles oscillating and quantify it, which is amazing to me,” said senior author Alexandra J. Golby, MD, of the Departments of Neurosurgery and Radiology at Brigham and Women’s Hospital in Boston. “They put these little microphones, which are called hydrophones, inside the helmet with water, and they listen for those frequencies and how much is coming out. The application of the focused ultrasound is actually many, many, many applications — it’s happening very quickly, multiple times — and they can kind of listen to each one, and it actually moves through our prescribed area one dot at a time.”

Taken together, the dots create a dose map, she said.

Dosing is important not only for knowing how to open the BBB but also for keeping the microbubbles from causing damage, Rezai said.

“If you give too much dose, you can burst the bubbles, and that causes hemorrhage. So you don’t want to open up the vessel too much,” he explained.

A Long Road of Approvals

The research and regulatory path has, of course, been a winding one. It wasn’t just a matter of letting the FDA know you’re going to improve the way existing chemotherapies are delivered to the brain.

There was new device approval. And there was approval for, essentially, three new drugs: intravenous microbubbles, gadolinium as an MRI contrast agent to ascertain the microbubble effect, and the chemotherapy itself. In the middle was a rising concern about a phenomenon known as gadolinium trapping, Woodworth said, so the team redesigned a trial to use focused ultrasound before surgery so they could demonstrate how treatments affected brain sections that were planned to be removed anyway.

The dose data came from a trial treating patients with high-grade glioma with monthly adjuvant temozolomide using MB-FUS, through which Woodworth said the experimental approach appeared ready for standardization.

“We asked, ‘Can we create a closed feedback loop control system that allows us to really understand what’s happening in real time?’” Woodworth recalled. “Can we create a power cycling system that allows us to create a more robust, reproducible treatment in

these regions that are, in the end, quite heterogeneous — they have different blood vessel densities, different white-to-gray matter ratios, just lots of differences in these regions."

Ultimately, he said, they had to be able to dose it "because for anything to really be meaningful in clinical practice, you have to have a dose response or at least have a dosing regimen with which to guide therapy."

The *Device* paper used data from 972 individual applications, collected across 58 treatment sessions for 23 patients with high-grade glioma at Brigham and Women's Hospital. Throughout the course of the trial, a software upgrade was made to enable sub-spot sonication, Golby said.

"They could basically turn up the power in the cold spots and turn it down in the hot spots because they could measure the acoustic emissions for each spot," she explained. "And part of the reason I think we were able to do this so well at the Brigham is that the director of the Focused Ultrasound Lab, Dr Nathan McDannold, and I sat side-by-side at the console for every single treatment we did."

"We did over 40 treatments," she added. "And I think that gave us a real opportunity to not just run people through a clinical trial but to use this as a real opportunity to try to understand where we could do better."

The newly published parameters are expected to supercharge the technology's scientific, clinical, and regulatory trajectory.

“It is still early days for this technology, but the more it is tested in the clinic and for a variety of diseases, such measurements will be critical for accelerating its clinical adoption, while ensuring safe and effective application,” said co-author and biomedical acoustics expert Costas D. Arvanitis, PhD, associate professor at Georgia Institute of Technology in Atlanta, whose team is studying how ultrasound frequency can be used to change BBB signaling to accumulate immune cells in brain tumors.

The framework in the *Device* paper is important because “it will allow comparisons among different hospitals as well as among different vendors,” Arvanitis said. “Ultimately, it will allow us to identify optimal settings for treating different diseases.”

What’s Next

An FDA application for liquid biopsy will likely be made by the end of the year, Woodworth said.

What he’s also watching, he cautiously admits, is how some of the patients in the 2023 temozolomide trial are doing.

“It is quite remarkable to see this number of patients still alive with what were very bad looking brain tumors and MRI scans,” he said, adding that “there’s no causal inference that you can necessarily draw from that. But what gets me excited about this is we know what we’re doing. We’re targeting specific areas of the brain with acoustic fields that we control. We know the dose of energy delivered to

those regions. We know the therapies that patients are receiving at the same time. We know the diagnosis that patients have from very rigorous molecular and histopathological analysis, and we know those patients are still alive."

It reminds him of why he started down this research path in the first place — because no matter how well a surgery goes, his ultimate goal is to find a better treatment for residual invasive disease.

"It is the beginning of something, and that's very exciting to me," he said. "So I'm going to continue to wake up every day and remember that and just keep pushing because these patients deserve better than two decades of the same thing."

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