



Penetrating the blood/brain barrier

MB-FUS aids brain cancer treatment.

THE BODY'S BLOOD/BRAIN BARRIER (BBB) is among its greatest defenses—and drawbacks, says Graeme F. Woodworth, MD, neurosurgeon at the University of Maryland School of Medicine in Baltimore.



MICHELE MEYER

Crossing that divide has long been his mission as a surgeon determined to save lives from glioblastoma, the deadliest cancer originating in the brain.

Aggressive and diffuse, glioblastoma's far-reaching tentacles often invade the brain before it's detected. Five-year survival odds are just 5.6% for adults over 40, who comprise most of the 12,000 Americans diagnosed each year, reports the American Brain Tumor Association.

"Up to now, glioblastomas have been a death sentence," says Woodworth, chair of neurosurgery at UMSOM and neurosurgeon-in-chief at the University of Maryland Medical Center. "The tumor cells often are cloaked and hidden behind the blood/brain barrier."

For now, only about 5% of medicine breaks through the barrier to reach the brain, he says.

"If I could remove every tumor cell from the brain surgically, I would," Woodworth says. "But the risk is too great of causing permanent neurological deficits, such as paralysis or vision loss. So how do we get to cancer cells that we can't remove with surgery?"

MB-FUS

University of Maryland partnered with Insightec, a Miami-based medical device maker, on a tool that unlocks the BBB gates: microbubble-booster transcranial-focused ultrasound, or MB-FUS.

Patients are fitted into a dome-like helmet containing 1,024 ultrasound elements that are coordinated to pass ultrasound beams throughout the skull, homing in on the diseased areas of the brain, Woodworth says.

MRI-guided ultra-low dose ultrasound uses soundwaves to activate the circulating microbubbles that concurrently are injected into the BBB. These bubbles expand, contract and vibrate, causing short-term mechanical forces on vessel walls, which opens the barrier temporarily.

"MB-FUS allows us to treat invasive disease earlier and in a more safe and effective manner," Woodworth says.

Insightec continually updates the technology while collaborating with Woodworth and other investigators, says Arjun Desai, MD, chief strategic innovation officer and CEO of Lotus Neuro. A study of 34 patients looked at MB-FUS safety, feasibility and early evidence of efficacy, as published in *Lancet Oncology* last December.

"Soundwaves don't involve any cutting or hospital stay, yet we're able to get therapies where they need to go," Desai says.

Benefits and limitations

The Insightec-led clinical study showed MB-FUS patients' lifespans were extended by 40%, when up to six monthly barrier-crossing treatments were given in addition to standard treatments. Overall, trial participants lived for more than 30 months, versus 19 months for the control group.

However, the MB-FUS device currently is tethered to an MRI scanner “and is not yet as simple and straightforward as we envision in the future,” Woodworth says. “We forecast an outpatient infusion-type therapy that takes an hour or less, instead of the few hours or more it can take now.”

Other challenges include determining the right ultrasound settings and standardizing the microbubbles.

The future

Woodworth and Desai see the combination of microbubbles and low-dose ultrasound as the door through which physicians also will be able to treat other diseases, including Alzheimer's, Huntington and Parkinson's diseases, ALS and possibly genetic disorders.

Elsewhere, Ali Rezai, MD, executive chair of the Rockefeller Neuroscience Institute at West Virginia University, is exploring use of MB-FUS to clear brain plaque in Alzheimer patients via monthly infusions of the drug aducanumab.

Still other Insightec trials are exploring low-dose ultrasound to enable treatment of metastatic brain cancer originating in the lungs and immunotherapy for

autoimmune disorders.

Meanwhile, the researchers have asked the U.S. Food and Drug Administration to grant MB-FUS approval for compassionate use.

“We're at a tipping point,” Desai says. “We've proven this technology is safe and are starting to show we can change the outcome of these diseases.” •

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