

# THE WALL STREET JOURNAL.

## THE FUTURE OF EVERYTHING

### New Ultrasound Therapy Could Help Treat Alzheimer's, Cancer

Sound waves combined with tiny bubbles in the bloodstream can push drugs into the brain and tough-to-reach tumors



French company Carthera has developed an ultrasound device to treat brain cancer. Shown here in a rendering, it works with tiny bubbles injected into the bloodstream to help drugs penetrate where they are needed. CARTHERA

*By Denise Roland*

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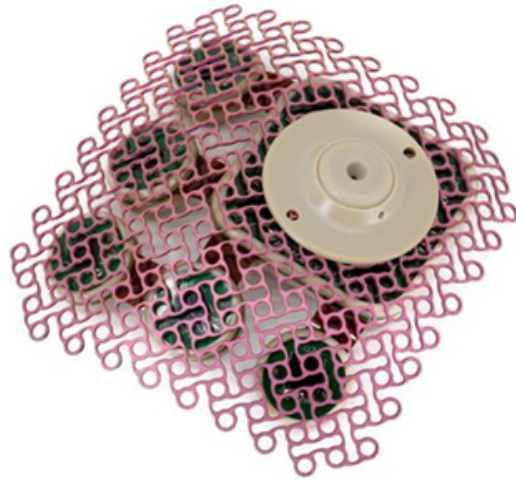
Ultrasound, the decades-old technology known for giving early glimpses of unborn babies, could hold a key to a problem that has long challenged drug developers: getting medicines to hard-to-reach places to treat diseases like Alzheimer's and cancer.

A cutting-edge approach that combines ultrasound waves with tiny bubbles of inert gas injected into the bloodstream can get more chemotherapy to tumor cells and enable drugs to breach one of the most stubborn frontiers in the human body—the blood-brain barrier. It is also being explored as a new way to deliver gene therapy.

“There’s an extremely wide variety of where this sort of drug delivery or augmentation with ultrasound and bubbles can take us,” says Flemming Forsberg, professor of radiology and director of ultrasound physics at Thomas Jefferson University in Philadelphia. The effectiveness of drugs in treating diseases like cancer, Alzheimer's and Parkinson's is often limited by poor penetration into tissues, he says, whether in the brain or in tumors in other parts of the body.

#### Getting Medicine to the Site

To get to the places they are needed, many drugs must move from the bloodstream into surrounding tissue. The medicines have to travel through the thin walls of the capillaries, the body's smallest blood vessels, and reach the target cells. This is tougher in some parts of the body than others. Some tumors are surrounded by dense networks of connective tissue that are hard to penetrate. In the brain, the capillary-wall cells are so tightly packed that they form a barrier that the vast majority of drugs can't get through.



Carthera's ultrasound-emitting device for the brain is embedded in titanium mesh. PHOTO: CARTHERA

The new approach relies on targeted ultrasound waves that cause vibrations in tiny bubbles that are injected into the bloodstream. The resulting force—which some compare to the way an opera singer's voice can make a wine glass quiver and even shatter—disrupts the surrounding capillary walls and tissue, temporarily creating microscopic gaps that have been shown to ease the passage of drugs in early human studies.

Some key questions must be explored as research progresses into larger human studies, says Seung-Schik Yoo, a researcher at Brigham and Women's Hospital and associate professor of radiology at Harvard Medical School who has done work in this area. One is ensuring that the disruption doesn't cause any lasting damage to tissues. Another is figuring out how frequently the procedure can be applied—and if there is a limit to the number of applications.

The procedure takes place during drug dosing or soon after. Typically, the microbubbles are injected intravenously while ultrasound, similar to the type used for fetal imaging, is applied at the target site for around five minutes. In one cancer trial, for instance, the microbubbles and ultrasound are administered around an hour after chemotherapy begins, so that the drug is at a high concentration in the blood at the time of the procedure.

While the microbubbles flow throughout the bloodstream, the disruption in tissue only occurs in the part of the body exposed to the ultrasound wave. The effect is temporary, lasting for as little as an hour, and the microbubbles remain in the blood for only around five minutes. The tiny size of the bubbles means they don't pose a risk of causing dangerous blockages in blood vessels, researchers say.

The component technologies aren't new.

Ultrasound has been used in medicine for more than half a century. Since the 1990s, microbubbles injected into the bloodstream have been widely used as a contrast agent to enhance images created by diagnostic ultrasound. Scientists observed that ultrasound causes these bubbles to resonate and saw the potential for that force to aid drug delivery. In 2001, scientists at Harvard Medical School demonstrated that ultrasound plus microbubbles could open the blood-brain barrier in rabbits. In the years since, scientists have tested the approach in many types of animals, building up early evidence that it could boost drug uptake and lead to meaningful improvements like greater tumor shrinkage in cancer.

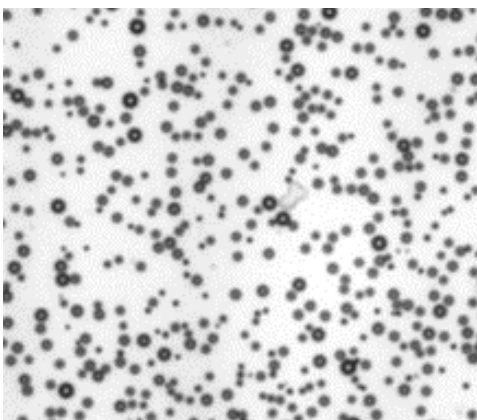
## Treatment for Brain Cancer

Now early human trials are producing encouraging results. In a small study of patients with glioblastoma—a type of brain cancer—researchers found that using the technology in treatment with carboplatin, a powerful chemotherapy, resulted in six times the amount of the drug in brain tissue that was exposed to the targeted ultrasound compared with unexposed brain tissue. In patients treated with paclitaxel, another cancer drug, levels were 3.7 times higher where the procedure was applied. Under normal circumstances, both drugs are seldom used to treat brain cancer because so little can get across the blood-brain barrier, according to Adam Sonabend, associate professor of neurological surgery at Northwestern University, who was involved in the trial.

In the glioblastoma trial, a small device developed by French company Carthera was used to avoid the difficulty of passing ultrasound through the skull bone, which weakens the power of the sound waves, according to the company's chief scientific officer Michael Canney. The ultrasound emitting device is embedded in titanium mesh used to reconstruct a small gap in the skull after surgery to remove the tumor, and sits directly above the brain. It emits ultrasound waves when connected to a power source via a syringe-like mechanism. The bubbles and the drugs are injected into the arm by intravenous infusion. Exact Therapeutics, a Norwegian company, recently told investors that liver tumors in two patients in a Phase 1 clinical trial that were exposed to ultrasound plus microbubbles during chemotherapy shrank more than those without the ultrasound. The trial is still under way at the Royal Marsden Hospital in London, and the results haven't yet been peer-reviewed.

The company has developed a formulation of microbubbles mixed with tiny oil droplets. When exposed to a particular frequency of ultrasound, they combine to temporarily form slightly larger bubbles in capillaries near the target tissue. They press directly against the capillary walls and stay there for longer, strengthening and prolonging the disruptive effects that allow drugs to pass into the target tissue, according to Exact Therapeutics Chief Executive Per Walday.

## Avenue for Gene Therapy



San Francisco-based SonoThera is developing a technology that uses microbubbles and ultrasound to deliver gene therapies. PHOTO: SONOTHERA

Another potential application of the new ultrasound approach is in gene therapy. Now, gene therapies rely on stripped-down viruses to carry and insert genetic material into target cells. A shortcoming of that approach is that the virus generates an immune response, so any repeat dose would be quickly destroyed by the body's defenses. Another limitation of viral vectors is that they can only carry genes up to a certain size. Animal studies suggest that ultrasound plus microbubbles could enable genetic material to pass into target cells without a viral carrier. **San Francisco-based startup SonoThera is developing** the technology with the aim of starting a Phase 1 clinical trial in 2025, the company's Chief Executive Kenneth Greenberg says.

An important area of work has been fine-tuning the size and shape of the ultrasound waves to bring about the right level of vibration for the target tissue in question, Greenberg says. “Much like a symphony, there is a complexity of different sounds and harmonics and amplitudes and timing that can be delivered through ultrasound,” he says. “The new twist is how you optimize the acoustics to maximize delivery for specific target organs.”

Ultrasound research could open up many new opportunities, say those involved. “This is just the beginning,” says Carthera’s Canney. With this technology, he says, doctors can revisit many drugs that have performed poorly in the past and ask: “Is it the drug, or just that we’re not getting the drug there?”

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