Biodegradable ultrasound opens the blood-brain barrier

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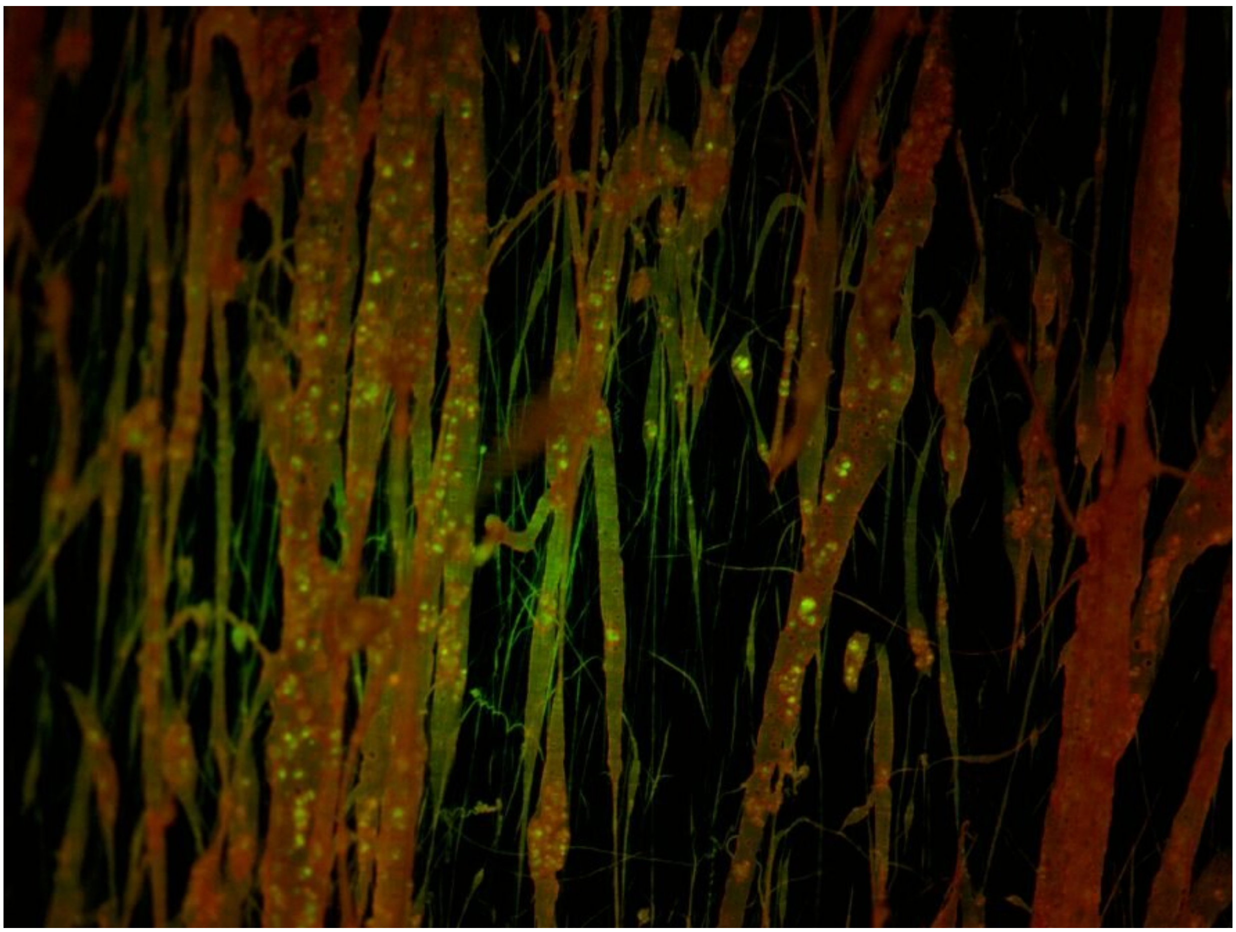

Nanofibers of glycine spun with polycaprolactone (PCL). Credit: Meysam T. Chorsi et al

A new, biodegradable ultrasound far more powerful than previous devices could make brain cancers more treatable, University of Connecticut researchers report in the June 14 issue of *Science Advances*.

Brain cancer affects more than 24,000 people in the US every year, and more than 18,000 Americans will die of one in 2023, according to the American Cancer Society.

When someone is diagnosed with a cancerous brain tumor, it is usually removed surgically and then chemotherapy is used to mop up the remaining cancer cells left behind. But brain cancers are particularly resistant to chemotherapy because the lining of the blood vessels prevents large molecules that could potentially harm the brain from passing through.

These also prevent useful chemo-drugs and other therapeutics from killing brain cancer cells and treating other brain diseases. One safe and effective way to get past the blood-brain barrier, as it's known, is to use ultrasound to jiggle cells enough to open pores large enough to allow the medicine to pass through.

But getting ultrasound through the thick human skull is not easy. Generally, multiple powerful ultrasound devices must be strategically placed around the skull and carefully focused on the site of the tumor with an MRI machine immediately after chemotherapy is administered in the hospital.

The process takes five or six hours and the powerful ultrasound can be damaging to tissue. It is rarely done more than once, even though most patients with aggressive brain cancers receive chemotherapy for months. Applying ultrasound every time the patient received chemotherapy would be much more effective. But because the MRI-ultrasound process is so cumbersome, it is rarely performed.

"We can avoid all of that by using an implanted device" within the brain itself, says biomedical engineer Thanh Nguyen. "We can repeatedly use it, allowing chemo to penetrate the brain and kill off tumor cells." There is already an implantable ultrasound device commercially available, but it is made of ceramic materials that are potentially toxic and must be surgically removed after treatment is finished.

Nguyen's lab specializes in biodegradable, piezoelectric polymers. Piezoelectric means that a material vibrates when a small electrical current runs through it. They had constructed a safe, biodegradable piezoelectric ultrasound brain implant before, but it wasn't as powerful as the traditional piezoelectric ceramics. So the Nguyen lab with graduate students Thinh T. Le and Meysam Chorsi, who is co-advised by Engineering Professor Horea Ilies and Engineering Dean Kazem Kazerounian, along with postdoc Feng Lin, used a totally new technique to produce a biodegradable polymer ultrasound just as powerful as those made of ceramics.

The team wanted to use crystals of glycine, an amino acid that is a common protein in the body and has been recently found to be strongly piezo-electric. Glycine is safe and biodegradable, but too much so; it quickly dissolves in water. Glycine piezoelectric crystals are also brittle and easily shatter, making handling the material and fabricating it into a useful ultrasound device extremely challenging.

The researchers came up with a novel solution. They grew glycine crystals and then intentionally shattered them into pieces just a few hundred nanometers in size. They then spun them (under high voltage in a process called electrospinning) with polycaprolactone (PCL), a biodegradable polymer, to make piezoelectric films composed of nanofibers of glycine and PCL.

Under a small driven voltage (~ 0.15 Vrms), the film can generate ultrasound at 334 kilo-Pascals, about the same as a ceramic ultrasound brain implant. The team coats the glycine-PCL film in other biodegradable polymers to protect it. Poly-L-Lactide (PLLA), one possible coating, takes approximately six weeks to break down.

The researchers tested the device in mice with brain cancer. They treated the mice with PTX (paclitaxel), a potent chemotherapy chemical that is effective against brain cancer but difficult to get past the blood-brain barrier. The glycine-PCL ultrasound successfully enabled PTX to bypass the blood-brain-barrier—the tumors shrank and the treatment doubled the lifetime of mice with brain cancer compared to those mice who received no treatment.

The combined glycine-PCL ultrasound + PTX treatment was also much more effective for the mice than treating with PTX alone, or PTX and ultrasound from the original, less powerful version of the Nguyen lab's biodegradable ultrasound device, based on PLLA.

In addition to the aforementioned therapeutic efficacy, the team has already done a six-month safety look at the device implanted inside the brain, and found it had no adverse effects on the health of the mice. They will now begin testing safety and efficacy in large animals.

More information: Meysam T. Chorsi et al, Highly piezoelectric, biodegradable, and flexible amino acid nanofibers for medical applications, *Science Advances* (2023). DOI: 10.1126/sciadv.adg6075

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