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Drug delivery platform leverages air-filled protein nanostructures and uses sound for targeting

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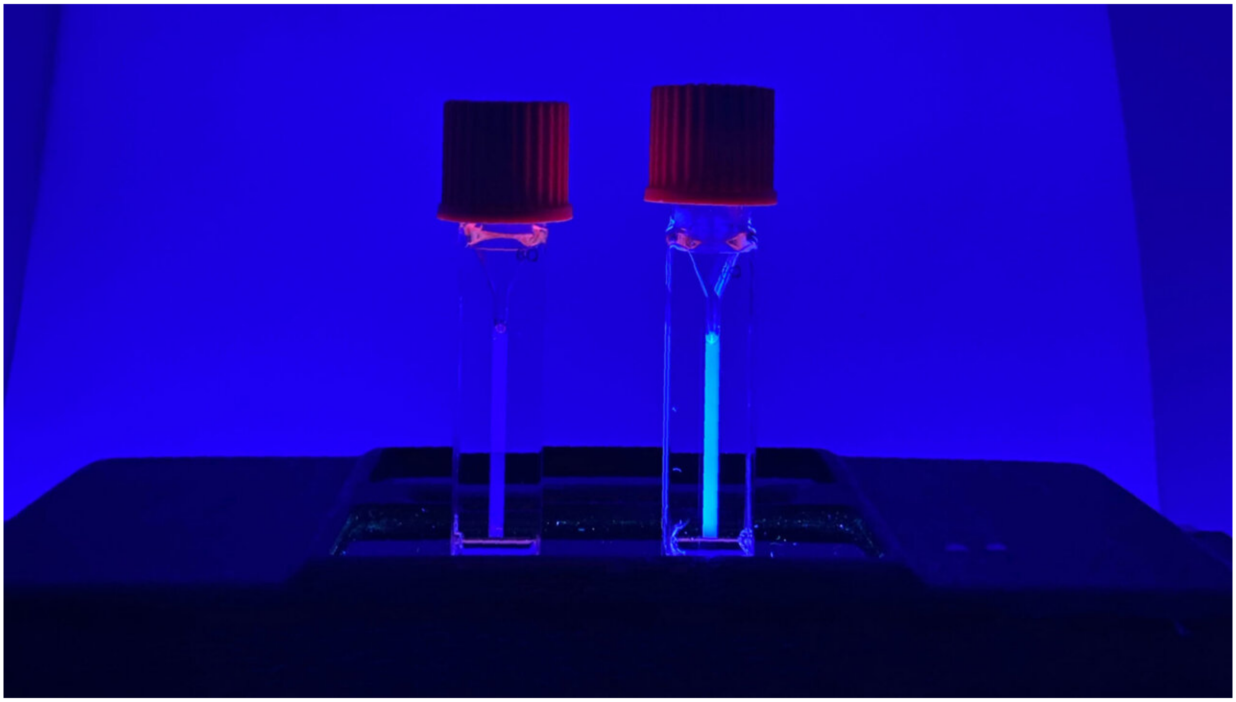


The vial at the left contains a solution with a fluorescent pigment bound within a mechanophore. At right, the pigment has been released from the mechanophore with ultrasound. Credit: Caltech

Chemotherapy as a treatment for cancer is one of the major medical success stories of the 20th century, but it's far from perfect. Anyone who has been through chemotherapy or who has had a friend or loved one go through it will be familiar with its many side effects: hair loss, nausea, weakened immune system, and even infertility and nerve damage.

This is because chemotherapy drugs are toxic. They're meant to kill cancer cells by poisoning them, but since cancer cells derive from healthy cells and are substantially similar to them, it is difficult to create a drug that kills them without also harming healthy tissue.

But now a pair of Caltech research teams have created an entirely new kind of drug delivery system, one that they say may finally give doctors the ability to treat cancer in a more targeted way. The system employs drugs that are activated by ultrasound—and only right where they are needed in the body.

The system was developed in the labs of Maxwell Robb, assistant professor of chemistry, and Mikhail Shapiro, Max Delbrück Professor of Chemical Engineering and Medical Engineering and Howard Hughes Medical Institute investigator.

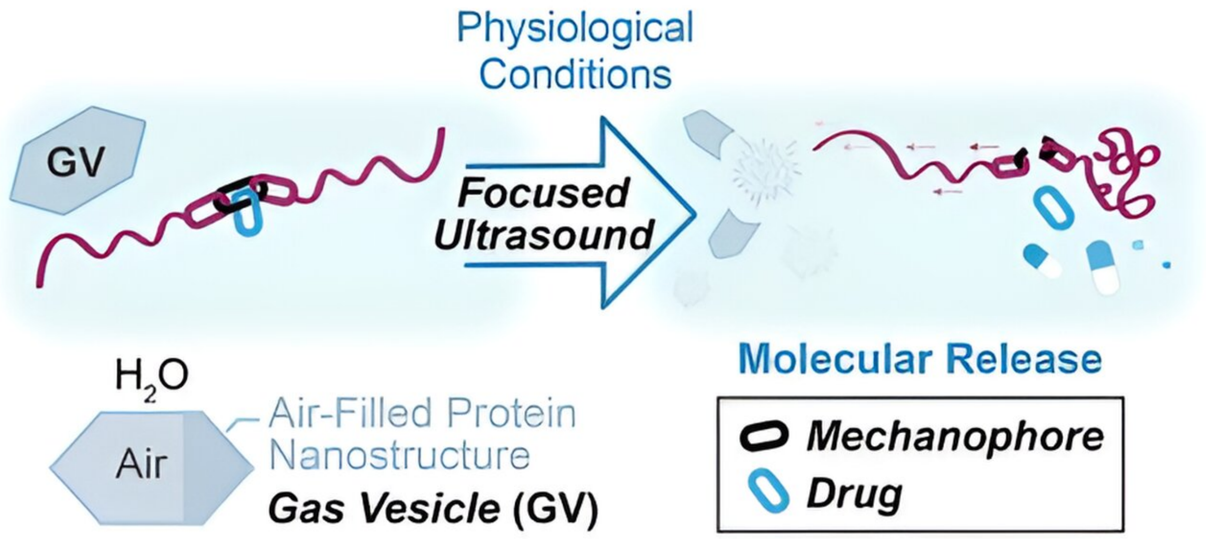
In a paper appearing in the journal *Proceedings of the National Academy of Sciences*, the researchers show how they combined elements from each of their specialties to create the platform. The paper is titled "Remote Control of Mechanochemical Reactions Under Physiological Conditions Using Biocompatible Focused Ultrasound."

Working collaboratively, the two research teams married gas vesicles (air-filled capsules of protein found in some bacteria) and mechanophores (molecules that undergo a chemical change when subjected to physical force). Shapiro's lab has previously used gas vesicles in conjunction with ultrasound to image individual cells and precisely move cells around.

Robb's lab, for its part, has created mechanophores that change color when stretched, making them useful for detecting strain in structures, and other mechanophores that can release a smaller molecule, including a drug, in response to a mechanical stimulus. For the new work, they devised a way to use ultrasound waves as that stimulus.

"We've been thinking about this for a really long time," Robb says. "It started when I first came to Caltech and Mikhail and I started having conversations about the mechanical effects of ultrasound."

As they began researching the combination of mechanophores and ultrasound, they discovered a problem: Ultrasound could activate the mechanophores, but only at an intensity so strong that it also damaged neighboring tissues. What the researchers needed was a way to focus the energy of the ultrasound right where they wanted it. It turned out that Shapiro's gas vesicle technology provided the solution.



In the presence of ultrasound, gas vesicles rupture, and in doing so, break apart molecules known as mechanophores that release a smaller, desired molecule. Credit: Caltech

In his previous work, Shapiro made use of the vesicles' tendency to vibrate or "ring" like a bell when bombarded with ultrasound waves. In the current research, however, the vesicles are rung so hard that they break, which focuses the ultrasound energy. The vesicles effectively become tiny bombs whose explosions activate the mechanophore.

"Applying force through ultrasound usually relies on very intense conditions that trigger the implosion of tiny dissolved gas bubbles," says Molly McFadden, Ph.D., study co-author. "Their collapse is the source of mechanical force that activates the mechanophore. The vesicles have heightened sensitivity to ultrasound. Using them, we found the same mechanophore activation can be achieved under much weaker ultrasound."

Yuxing Yao, a postdoctoral scholar research associate in Shapiro's lab, says this is the first time that focused ultrasound has been able to control a specific chemical reaction in a biological setting.

"Previously ultrasound has been used to disrupt things or move things," Yao says. "But now it's opening this new path for us using mechanochemistry."

So far, the platform has only been tested under controlled laboratory conditions, but in the future, the researchers plan to test it in living organisms.

More information: Yuxing Yao et al, Remote control of mechanochemical reactions under physiological conditions using biocompatible focused ultrasound, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2309822120.
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