# Focused delivery for brain cancers

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Hong Chen, assistant professor of biomedical engineering in the School of Engineering & Applied Science and assistant professor of radiation oncology at Washington University School of Medicine in St. Louis. Credit: Washington University in St. Louis

A person's brainstem controls some of the body's most important functions, including heart beat, respiration, blood pressure and swallowing. Tumor growth in this part of the brain is therefore twice as devastating. Not only can such a growth disrupt vital functions, but operating in this area is so risky, many medical professionals refuse to consider it as an option.

New, interdisciplinary research in Washington University in St. Louis has shown a way to target drug delivery to just that area of the brain using noninvasive measures, bolstered by a novel technology: focused ultrasound.

The research comes from the lab of Hong Chen, assistant professor of biomedical engineering in the School of Engineering & Applied Science and assistant professor of radiation oncology at Washington University School of Medicine. Chen has developed a novel way in which ultrasound and its contrast agent—consisting of tiny bubbles—can be paired with intranasal administration, to direct a drug to the brainstem.

The research, which also included faculty from the Mallinckrodt Institute of Radiology and the Department of Pediatrics at the School of Medicine, along with the Department of Energy, Environmental & Chemical Engineering in the School of Engineering & Applied Science, was published online this week and will be in the Sept. 28 issue of the *Journal of Controlled Release*.

This technique may bring medicine one step closer to curing brain-based diseases such as diffuse intrinsic pontine gliomas (DIPG), a childhood brain cancer with a five-year survival rate of a scant two percent, a dismal prognosis that has remained unchanged over the past 40 years. (To add perspective, the most common childhood cancer, acute lymphoblastic leukemia, has a five-year survival rate of nearly 90 percent).

"Each year in the United States, there are no more than 300 cases," Chen said. "All pediatric diseases are rare; luckily, this is even more rare. But we cannot count numbers in this way, because for kids that have this disease and their families, it is devastating."

Chen's technique combines Focused UltraSound with IntraNasal delivery, (FUSIN). The intranasal delivery takes advantage of a unique property of the olfactory and trigeminal nerves: they can carry nanoparticles directly to the brain, bypassing the blood brain barrier, an obstacle to drug delivery in the brain.

This unique capability of intranasal delivery was demonstrated last year by co-authors Ramesh Raliya, research scientist, and Pratim Biswas, assistant vice chancellor and chair of the Department of Energy, Environmental & Chemical Engineering and the Lucy & Stanley Lopata Professor, in their 2017 publication in Scientific Reports.

"At the beginning, I couldn't even believe this could work," Hong said of delivering drugs to the brain intranasally. "I thought our brains are fully protected. But these nerves actually directly connect with the brain and provide direct access to the brain."

While nasal brain drug delivery is a huge step forward, it isn't yet possible to target a drug to a specific area. Chen's targeted ultrasound technique is addressing that problem.

When doing an ultrasound scan, the contrast agent used to highlight images is composed of microbubbles. Once injected into the bloodstream, the microbubbles behave like red blood cells, traversing the body as the heart pumps.

Once they reach the site where the ultrasound wave is focused, they do something unusual.

"They start to expand and contract," Chen said. As they do so, they act as a pump to the surrounding blood vessels as well as the perivascular space—the space surrounding the blood vessels.

"Consider the blood vessels like a river," Chen said. "The conventional way to deliver drugs is to dump them in the river." In other parts of the body, the banks of the river are a bit "leaky," Chen said, allowing the drugs to seep into the surrounding tissue. But the blood brain barrier, which forms a protective layer around blood vessels in the brain, prevents this leakage, particularly in the brains of young patients, such as those with with DIPG.

"We will deliver the drug from the nose to directly outside the river," Chen said, "in the perivascular space."

Then, once ultrasound is applied at the brain stem, the microbubbles will begin to expand and contract. The oscillating microbubbles push and pull, pumping the drug toward the brainstem. This technique also addresses the problem of drug toxicity—the drugs will go directly to the brain instead of circulating through the whole body. In collaboration with Yongjian Liu, an associate professor of radiology, and Yuan-Chuan Tai, an associate professor of radiology, Chen used positron emission tomography (PET scan) to verify that there was minimal accumulation of intranasal-administered nanoparticles in major organs, including lungs, liver, spleen, kidney and heart.

So far, Chen's lab has had success using their technique in mice for the delivery of gold nanoclusters made by the team led by Liu.

"The next step is to demonstrate the therapeutic efficacy of FUSIN in the delivery of chemotherapy drugs for the treatment of DIPG," said Dezhuang Ye, lead author of the paper, who is Chen's graduate student from the Department of Mechanical Engineering & Materials Science. The lab has also teamed up with Biswas to develop a new aerosol nasal delivery device to scale up the technique from a mouse to a large animal model.

Chen's lab collaborated on this research with pediatric neuro-oncologist

Joshua Rubin, MD, Ph.D., a professor of pediatrics at the School of Medicine who treats patients at St. Louis Children's Hospital. Chen said the team hopes to translate the findings of this study into clinical trials for children with DIPG.

There are difficulties ahead, but Chen believes researchers will need to continue to innovate when it comes to solving such a difficult problem as treating DIPG.

## A targeted inspiration

Hong Chen's lab collaborated with Joshua Rubin, MD, Ph.D., a professor of pediatrics at the School of Medicine on this research. And it all started with a couple of colleagues talking one day:

"My work in this field started with a conversation with him," Chen said. "He said, 'Wow, this would be a perfect technique for treating this deadly disease.' Without him to point me in this direction, I probably wouldn't have known this application existed.

"That's why I consider the Washington University environment, and the School of Engineering & Applied Science, so unique. It provides you so much opportunity to work with people from different backgrounds. It allowed me to expand my research scope and to be able to work on clinically relevant questions."

**More information:** Dezhuang Ye et al, Focused ultrasound combined with microbubble-mediated intranasal delivery of gold nanoclusters to the brain, *Journal of Controlled Release* (2018). DOI: 10.1016/j.jconrel.2018.07.020

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