'Nanobubbles' plus chemotherapy equals single-cell cancer targeting

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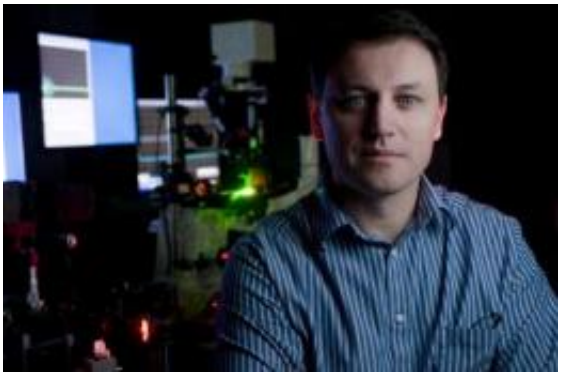

This is Dmitri Lapotko. Credit: Jeff Fitlow/Rice University

Using light-harvesting nanoparticles to convert laser energy into "plasmonic nanobubbles," researchers at Rice University, the University of Texas MD Anderson Cancer Center and Baylor College of Medicine (BCM) are developing new methods to inject drugs and genetic payloads directly into cancer cells. In tests on drug-resistant cancer cells, the researchers found that delivering chemotherapy drugs with nanobubbles was up to 30 times more deadly to cancer cells than traditional drug treatment and required less than one-tenth the clinical dose.

"We are delivering cancer drugs or other genetic cargo at the single-cell level," said Rice's Dmitri Lapotko, a biologist and physicist whose plasmonic nanobubble technique is the subject of four new peer-reviewed studies, including one due later this month in the journal

Biomaterials and another published April 3 in the journal PLoS ONE. "By avoiding healthy cells and delivering the drugs directly inside cancer cells, we can simultaneously increase drug efficacy while lowering the dosage."

Delivering drugs and therapies selectively so they affect cancer cells but not healthy cells nearby is a major obstacle in drug delivery. Sorting cancer cells from healthy cells has been successful, but it is both time-consuming and expensive. Researchers have also used nanoparticles to target cancer cells, but nanoparticles can be taken up by healthy cells, so attaching drugs to the nanoparticles can also kill healthy cells.

Rice's nanobubbles are not nanoparticles; rather, they are short-lived events. The nanobubbles are tiny pockets of air and water vapor that are created when laser light strikes a cluster of nanoparticles and is converted instantly into heat. The bubbles form just below the surface of cancer cells. As the bubbles expand and burst, they briefly open small holes in the surface of the cells and allow cancer drugs to rush inside. The same technique can be used to deliver gene therapies and other therapeutic payloads directly into cells.

This method, which has yet to be tested in animals, will require more research before it might be ready for human testing, said Lapotko, faculty fellow in biochemistry and cell biology and in physics and astronomy at Rice.

The *Biomaterials* study due later this month reports selective genetic modification of human T-cells for the purpose of anti-cancer cell therapy. The paper, which is co-authored by Dr. Malcolm Brenner, professor of medicine and of pediatrics at BCM and director of BCM's Center for Cell and Gene Therapy, found that the method "has the potential to revolutionize drug delivery and gene therapy in diverse applications."

"The nanobubble injection mechanism is an entirely new approach for drug and gene delivery," Brenner said. "It holds great promise for selectively targeting cancer cells that are mixed with healthy cells in the same culture."

Lapotko's plasmonic nanobubbles are generated when a pulse of laser light strikes a plasmon, a wave of electrons that sloshes back and forth across the surface of a metal nanoparticle. By matching the wavelength of the laser to that of the plasmon, and dialing in just the right amount of laser energy, Lapotko's team can ensure that nanobubbles form only around clusters of nanoparticles in cancer cells.

Using the technique to get drugs through a cancer cell's protective outer wall, or cell membrane, can dramatically improve the drug's ability to kill the cancer cell, as shown by Lapotko and MD Anderson's Xiangwei Wu in two recent studies, one in Biomaterials in February and another in *Advanced Materials* in March.

"Overcoming drug resistance represents one of the major challenges in cancer treatment," said Wu. "Targeting plasmonic nanobubbles to cancer cells has the potential to enhance drug delivery and cancer-cell killing."

To form the nanobubbles, the researchers must first get the gold nanoclusters inside the cancer cells. The scientists do this by tagging individual gold nanoparticles with an antibody that binds to the surface of the cancer cell. Cells ingest the gold nanoparticles and sequester them together in tiny pockets just below their surfaces.

While a few gold nanoparticles are taken up by healthy cells, the cancer cells take up far more, and the selectivity of the procedure owes to the fact that the minimum threshold of laser energy needed to form a nanobubble in a cancer cell is too low to form a nanobubble in a healthy cell.

More information: The research is funded by the National Institutes of Health and is described in the following recent papers:

-- "Cell-specific transmembrane injection of molecular cargo with gold nanoparticle-generated transient plasmonic nanobubbles," which is due for publication later this month in Biomaterials. Co-authors include Lapotko, Ekaterina Lukianova-Hleb and Daniel Wagner, all of Rice, and BCM's Brenner.
-- "Plasmonic nanobubble-enhanced endosomal escape processes for selective and guided intracellular delivery of chemotherapy to drug-resistant cancer cells," which appeared in the February issue of Biomaterials. Co-authors include Lapotko, Lukianova-Hleb, Andrey Belyanin and Shruti Kashinath, all of Rice, and MD Anderson's Wu.
-- "Plasmonic nanobubbles enhance efficacy and selectivity of chemotherapy against drug-resistant cancer cells," which was published online March 7 in the journal Advanced Materials. Co-authors include Lapotko and Lukianova-Hleb, both of Rice; Wu and Ren, both of MD Anderson; and Joseph Zasadzinski of the University of Minnesota.
-- "Improved cellular specificity of plasmonic nanobubbles versus nanoparticles in heterogeneous cell systems," which was published online April 3 in PLoS ONE. Co-authors include Laptoko, Wagner, Lukianova-Hleb, Daniel Carson, Cindy Farach-Carson, Pamela Constantinou, Brian Danysh and Derek Shenefelt, all of Rice; Wu and Xiaoyang Ren, both of MD Anderson; and Vladimir Kulchitsky of the National Academy of Science of Belarus.

Provided by Rice University