'Quadrapeutics' works in preclinical study of hard-to-treat tumors

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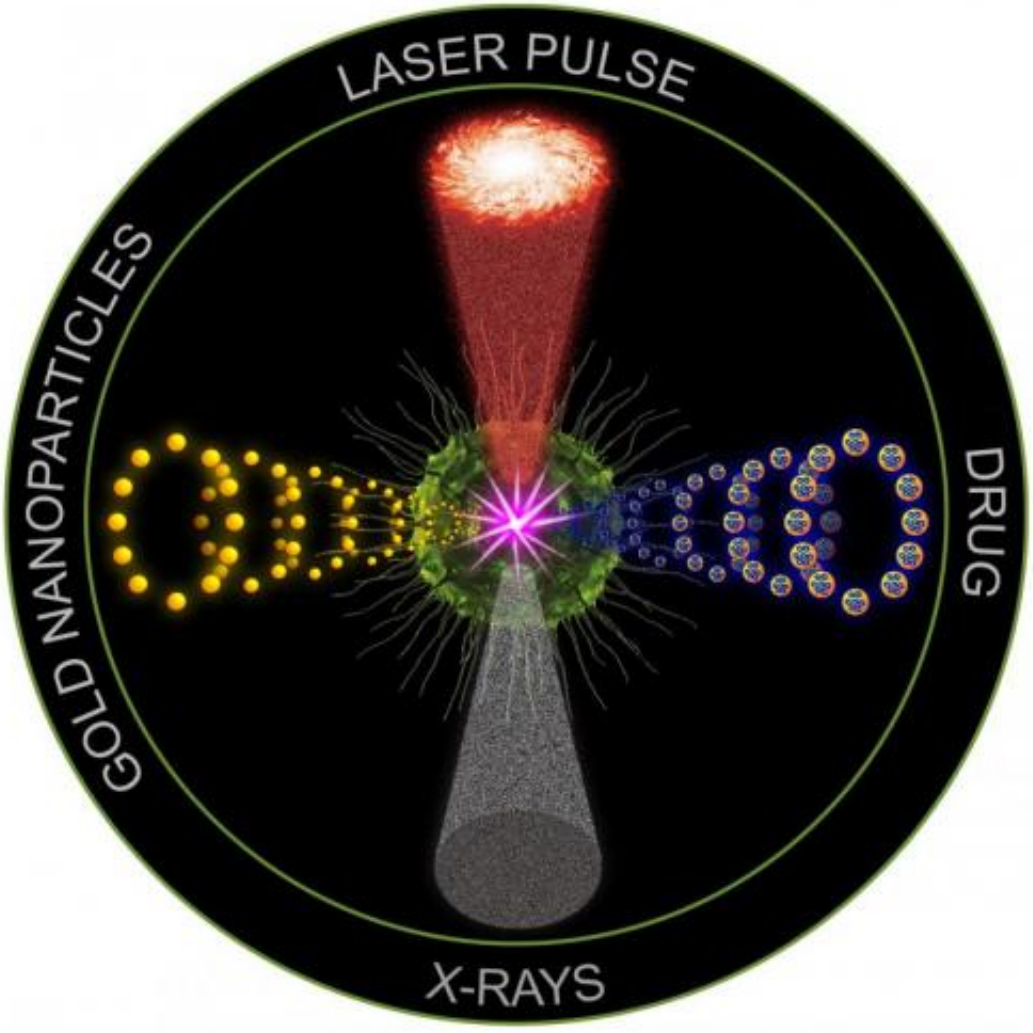

The first preclinical study of the anti-cancer technology "quadrapeutics" found it to be 17 times more efficient than conventional chemoradiation therapy against aggressive, drug-resistant head and neck tumors. Credit: D. Lapotko/Rice University

The first preclinical study of a new Rice University-developed anti-cancer technology found that a novel combination of existing clinical treatments can instantaneously detect and kill only cancer cells—often by blowing them apart—without harming surrounding normal organs. The research, which is available online this week *Nature Medicine*, reports that Rice's "quadrapeutics" technology was 17 times more efficient than conventional chemoradiation therapy against aggressive, drug-resistant head and neck tumors.

The work was conducted by researchers from Rice, the University of Texas MD Anderson Cancer Center and Northeastern University.

"We address aggressive cancers that cannot be efficiently and safely treated today," said Rice scientist Dmitri Lapotko, the study's lead investigator. "Surgeons often cannot fully remove tumors that are intertwined with important organs. Chemotherapy and radiation are commonly used to treat the residual portions of these tumors, but some tumors become resistant to chemoradiation. Quadrapeutics steps up when standard treatments fail. At the same time, quadrapeutics complements current approaches instead of replacing them."

Lapotko said quadrapeutics differs from other developmental cancer treatments in that it radically amplifies the intracellular effect of drugs and radiation only in cancer cells. The quadrapeutic effects are achieved by mechanical events—tiny, remotely triggered nano-explosions called "plasmonic nanobubbles." Plasmonic nanobubbles are non-stationary vapors that expand and burst inside cancer cells in nanoseconds in response to a short, low-energy laser pulse. Plasmonic nanobubbles act as a "mechanical drug" against cancer cells that cannot be surgically removed and are otherwise resistant to radiation and chemotherapy.

In prior studies, Lapotko showed he could use plasmonic nanobubbles alone to literally blow cells apart. In quadrapeutics, his team is using them to detect and kill cancer cells in three ways. In cancer cells that survive the initial explosions, the bursting nanobubbles greatly magnify the local doses of both chemotherapy drugs and radiation. All three effects—mechanical cell destruction, intracellular drug ejection and radiation amplification—occur only in cancer cells and do not harm vital healthy cells nearby.

To administer quadrapeutics, the team uses four clinically approved components: chemotherapy drugs, radiation, near-infrared laser pulses of low energy and colloidal gold.

"Quadrapeutics shifts the therapeutic paradigm for cancer from materials—drugs or nanoparticles—to mechanical events that are triggered on demand only inside cancer cells," Lapotko said. "Another strategic innovation is in complementing current macrotherapies with microtreatment. We literally bring surgery, chemotherapies and radiation therapies inside cancer cells."

The first component of quadrapeutics is a low dose of a clinically validated chemotherapy drug. The team tested two: doxorubicin and paclitaxel. In each case, the scientists used encapsulated versions of the drug that were tagged with antibodies designed to target cancer cells. Thanks to the magnifying effect of the plasmonic nanobubbles, the intracellular dose—the amount of the drug that is active inside cancer cells—is very high even when the patient receives only a few percent of the typical clinical dose.

The second component is an injectable solution of nontoxic gold colloids, tiny spheres of gold that are thousands of times smaller than a living cell. Quadrapeutics represents a new use of colloidal gold, which has been used for decades in the clinical treatment of arthritis. In

quadrapeutics, the gold colloids are tagged with cancer-specific clinically approved antibodies that cause them to accumulate and cluster together inside cancer cells. These gold "nanoclusters" do nothing until activated by a laser pulse or radiation.

The third quadrapeutic component is a short near-infrared laser pulse that uses 1 million times less energy that a typical surgical laser. A standard endoscope delivers the laser pulse to the tumor, where the gold nanoclusters convert the laser energy into plasmonic nanobubbles.

The fourth component is a single, low dose of radiation. The gold nanoclusters amplify the deadly effects of radiation only inside cancer cells, even when the overall dose to the patient is just a few percent of the typical clinical dose.

"What kills the most-resistant cancer cells is the intracellular synergy of these components and the events we trigger in cells," Lapotko said. "This synergy showed a 100-fold amplification of the therapeutic strength of standard chemoradiation in experiments on cancer cell cultures."

In the *Nature Medicine* study, the team tested quadrapeutics against head and neck squamous cell carcinoma (HNSCC), an aggressive and lethal form of cancer that had grown resistant to both chemotherapy drugs and radiation. Quadrapeutics proved so deadly against HNSCC tumors that a single treatment using just 3 percent of the typical drug dose and 6 percent of the typical radiation dose effectively eliminated tumors in mice within one week of the administration of quadrapeutics.

Lapotko, a faculty fellow in biochemistry and cell biology and in physics and astronomy, said he is working with colleagues at MD Anderson and Northeastern to move as rapidly as possible toward prototyping and a human clinical trial. In clinical applications, quadrapeutics will be applied as either a stand-alone or intra-operative procedure using

standard endoscopes and other clinical equipment and encapsulated drugs such as Doxil or Lipoplatin. Though the current study focused on head and neck tumors, Lapotko said quadrapeutics is a universal technology that can be applied for local treatment of various solid tumors, including other hard-to-treat types of brain, lung and prostate cancer. He said it might also prove especially useful for treating children due to its safety.

"The combination of aggressiveness and drug and radiation resistance is particularly problematic in tumors that cannot be fully resected, and new efficient solutions are needed," said Dr. Ehab Hanna, a surgeon and vice chair of the Department of Head and Neck Surgery at MD Anderson, who was not involved with the testing or development of quadrapeutics. "Technologies that can merge and amplify the effects of surgery, drugs and radiation at the cellular level are ideal, and the preclinical results for quadrapeutics make it a promising candidate for clinical translation."

More information: Paper: On-demand intracellular amplification of chemoradiation with cancer-specific plasmonic nanobubbles, dx.doi.org/10.1038/nm.3484

Provided by Rice University