

Gold by special delivery intensifies cancer-killing radiation

KINGSTON – Researchers from the University of Rhode Island and Brown University have demonstrated a promising new way to increase the effectiveness of radiation in killing cancer cells.

Building on research by URI Physics **PROFESSORS YANA RESHETNYAK** and **OLEG ANDREEV**, the new approach involves gold nanoparticles tethered to acid-seeking compounds called pHLIPs. The pHLIPs (pH low-insertion peptides) home in on the high acidity of malignant cells, delivering their nanoparticle passengers straight to the cells' doorsteps. The nanoparticles then act as tiny antennas, focusing the energy of radiation in the area directly around the cancer cells.

In a paper published April 13 in the *Proceedings of the National Academy of Sciences*, the research team shows that the approach substantially increases the cancer-killing power of radiation in lab tests.

"This study was a good proof of concept," said Michael Antosh, assistant professor in Brown's Institute for Brain and Neural Systems and the paper's lead author. "We're encouraged by our initial results and we're excited to take the next step and test this in mice."

The team is hopeful that the approach could ultimately improve radiation treatment for cancer patients. By increasing the effectiveness that a given dose of radiation has on cancer, the technique could reduce the overall radiation dose a patient requires, which would in turn reduce side effects. It could also increase the effectiveness of radiation at doses currently administered.

Reshetnyak and Andreev, along with Yale University Professor Donald Engelman, invented the pHLIP technology. They had previously developed pHLIPs as a potential delivery system for cancer drugs and diagnostic agents. Cancer cells are generally more acidic than healthy cells, and pHLIPs are natural acid-seekers.

"We previously demonstrated that

pHLIP-nanogold particles could find and accumulate in tumors established in mice," Reshetnyak said. "Now our task is to test if we can treat cancer by irradiating tumors with nanogold particles more efficiently in comparison with traditional radiation treatment."

Both theoretical and experimental work had shown that gold nanoparticles could intensify the effect of radiation. The particles absorb up to 100 times more radiation than tissue. Radiation causes the particles to release a stream of electrons into the area around them. If the particles were in close proximity to cancer cells, that stream of electrons would inflict damage on those cells.

"The idea here was to bring this all together, combining the nanoparticles with the delivery system and then irradiating them to see if it had the desired effect," said Leon Cooper, the Thomas J. Watson Sr. Professor of Science at Brown and one of the study's co-authors. Cooper, who shared the Nobel Prize in 1972 for explaining the behavior of electrons in superconductors, has been working for the last several years to better understand biological responses to radiation.

Gold is an especially good choice for amplifying radiation. When matter

is hit by radiation at certain energies, electrons are released through a process known as the photoelectric effect. But gold has an additional source of electron emission, known as the Auger effect, that results from the particular arrangement of electrons orbiting gold atoms. It's the effect of the Auger electrons that the researchers were working to maximize. Working out the quantitative details of the process involved a complex series of calculations and simulations.

Experiments showed that cancer cells irradiated in the presence of pHLIP-delivered gold had a 24-percent lower survival rate compared to those treated with radiation alone. The pHLIP samples had a 21-percent lower survival compared to irradiation with just gold but no pHLIPs. That suggests that the pHLIPs were effective in getting the gold close enough to the cells to do damage.

The next step, the researchers say, is to test the approach in a rodent model, which the team is planning to do soon.

"This work is a great example of successful collaboration between Brown and URI," Andreev said. "We hope that the results of this research moving forward will lead to clinical application of pHLIP-based nanotechnology." ♦

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