LOW DOSE, HIGH ALERT

A NEW RADIOTHERAPY WAKES UP THE IMMUNE SYSTEM

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Cancer cells look different from healthy cells. They are dusted with molecules that stick out like flags, which the immune system can often see and react to by destroying the cells. However, immune cells don't always detect the flags, allowing cancerous cells to divide and spread throughout the body.

Radiation treatment typically involves aiming an external beam of radiation at a tumor site to kill the cells. In the case of metastatic cancer, though, there are too many sites to irradiate this way, and the high dose of radiation poses a risk to healthy cells.

Ravi Patel, an MD, PhD radiation oncologist at the UPMC Hillman Cancer Center and assistant professor of radiation oncology and of bioengineering at Pitt, is taking a different approach. Instead of trying to eradicate all cancer cells with radiation, his lab is using low-dose radiopharmaceuticals that locate and kill some cells in a tumor and then alert the patient's own immune response to take care of the rest.

His work makes use of targeted delivery of radionuclides, called theranostics. The approach was pioneered by Saul Hertz in 1941 when he used radioactive iodine to combine imaging with therapy for thyroid cancer.

Here's how modern theranostics works: While traveling through the bloodstream, a targeting molecule searches for the molecular flags on cancer cells. It also carries a radionuclide, which emits radiation that can provide either imaging or treatment.

Patel notes that current radiopharmaceutical therapies can improve cancer patients' quality of life. He recalls a patient with metastatic prostate cancer who regained the ability to bend over and pick things up.

"These are small things," Patel says, "but for these individuals, it's a really big thing, because when you lose those functions, it can dramatically affect your life."

Still, Patel wanted to do more for patients with metastatic disease, which is why he began experimenting with using theranostics differently. His low-dose theranostics approach fights cancer from two angles: radiation and immunology. As cells die, they display molecular flags unique to dead cells, which wakes up the immune system and calls it to where cancer was hiding. After a series of treatments, the cumulative dose of radiation needed to eradicate a tumor can reach 150 to 200 gray (a unit for measuring absorbed ionizing radiation). But Patel and colleagues discovered that up to 100 times less radiation was needed to damage tumors enough to elicit an immune response—with minimal side effects from the radiation. The body was then able to destroy many of those previously hidden, or what are also known as "cold," tumors.

"When we stimulate an immune response and then give immunotherapies that tumors have become resistant to, we can cure many of these cancers," says Patel.

With collaborators at the University of Wisconsin, he showed the potential of this low-dose radiopharmaceutical treatment in animals and published the results in a 2021 paper in Science Translational Medicine.

Yet the approach can be honed even further. Cancer is unique to each patient, so there's variability in how well targeting molecules locate and differentiate cancerous cells from healthy cells. "Even though you're targeting this radionuclide to tumor cells, some do go to normal tissues," Patel notes. And targeted radionuclide therapy alone is often unable to cure cancer.

Patel aims to develop a personalized low-dose theranostics platform through which patients will receive the best dose and radiopharmaceutical to achieve high uptake in their tumors and little in healthy tissues. The platform would then direct the best combination of additional therapies.

Working with Pitt's nuclear medicine and radiation oncology groups, Patel is now preparing clinical trials to get the low-dose approach into the clinic.

"One of the nice things at Pitt," he says, "is that we have an attitude that we are here to treat patients, and we are going to work together and bring all our strengths together." ■