Radiation, meet cancer cell

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Radiation is a double-edged sword.

While ionizing radiation—the kind that knocks electrons off atoms—can cause cancer or even death, it can also save lives. Among other uses, ionizing radiation can destroy cancer cells, giving many sufferers the hope of relief from the painful effects of cancer.

That's the goal of ORNL's nuclear medicine program. In particular, these researchers are working to exploit radioisotopes that emit alpha radiation, a type of ionizing radiation that releases a lot of energy in a very small space.

"Alpha particles penetrate only to about a 10-cell diameter or 100 micrometers—about the thickness of a human hair," explained ORNL nuclear chemist Saed Mirzadeh. "If you can target a cell—if your targeting molecule is engineered correctly, and you put these radioisotopes on as a payload—then these radioisotopes kill that cell, that specific cell, and maybe 10 cells around it."

Alpha particles are one of three types of radiation, the other two being beta particles and gamma radiation. An alpha particle consists of two protons and two neutrons, making it essentially a helium nucleus. A beta particle, on the other hand, is a high-energy electron or positron, while gamma radiation is the highest-energy form of electromagnetic radiation, putting it in the same category as microwaves, radio waves, visible light and X-rays.

ORNL has two processes for producing alpha emitters such as actinium-225, actinium-227 and lead-212. In one process, targets are bombarded at the High Flux Isotope Reactor—or, in collaboration with other national laboratories, at an accelerator—while in the other, the isotopes are separated from nuclear waste. Mirzadeh and collaborators at institutions such as the University of Tennessee College of Medicine and Memorial Sloan Kettering Cancer Center in New York City then work on ways to get the isotopes to the cancers they must destroy.

Nuclear chemist Saed Mirzadeh. Image credit: Carlos Jones, ORNL

Sometimes the isotopes do the hard part—i.e., the targeting—themselves. That's the case with radium-223, which is marketed by Bayer as Xofigo. Radium-223 is a decay product of actinium-227 (currently produced at HFIR) and is used to treat prostate cancer that has spread to the bones. Because radium is chemically similar to calcium, the drug goes where calcium would go—that is, straight to bone cancer cells—and largely ignores other tissues, meaning it has few to no side effects.

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Mostly, however, isotopes do not target themselves. As researchers

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develop new treatments, they must overcome two major obstacles: directing the isotopes to cancer cells and keeping them from being metabolized along the way.

That second job goes to molecules known as ligands. Ligands act as baskets to hold alpha-emitting isotopes, preventing them from being hydrolyzed and excreted.

"What the ligand does is keep the metal ion intact inside this basket," Mirzadeh explained. "The body's proteins are very good at getting rid of metal ions. They just grab them and dispose of them through different mechanisms—through the liver, guts or kidneys. So we have to protect them so they don't hydrolyze."

The other job—delivering the isotope to cancer cells—goes to peptides, proteins that seek and attach to specific cells. When peptides, which have seen astonishing advances recently, are combined with the right isotope and basket molecule, they can deliver a dose of radiation selectively to cancer cells while bypassing healthy cells.

Beta and gamma radiation are also used to treat cancer, but Mirzadeh believes alpha-emitting isotopes are the future of radiation therapy. They can deliver a large amount of ionizing radiation to the targeted cells, rendering the cells unable to repair themselves. In addition, when combined with the right basket molecule and peptide, they are uniquely effective at finding and destroying the undetectable small tumors and micrometastases present in a spreading cancer.

"With all these, you don't know where the small tumors and micrometastases are," Mirzadeh explained. "If you know where the cancer cells are that you want to destroy, then of course you can knock them out, but you don't know where they are.

"Alpha emitters are about a thousand times more potent than the beta emitters. It's really clear from a scientific point of view."