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Attacking cancer with radioisotopes

Cutting-edge isotope science is shaping the future of precision medicine and cancer treatment

KEY POINTS

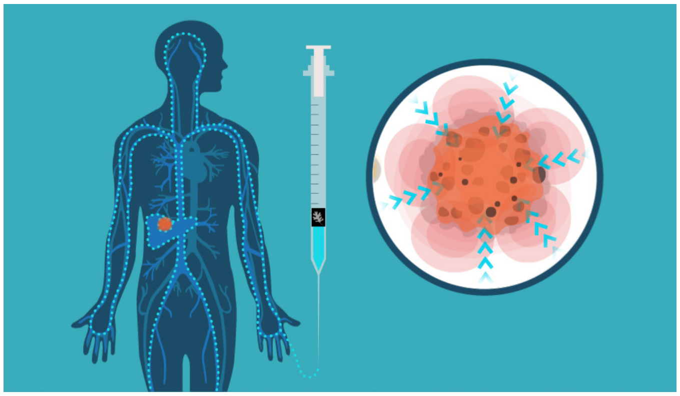
- **ORNL produces and supplies actinium-225, a rare isotope essential for targeted alpha therapy and vital to advancing cancer treatment research.**
- **Targeted alpha therapy attacks tumors while sparing healthy tissue, offering hope for treating cancers resistant to traditional therapies.**
- **Researchers are developing new delivery methods using chelators and nanoparticles to make treatments safer and more precise.**

Somewhere in America, a patient with cancer participating in a clinical trial receives an experimental drug — a treatment built on the hope of attacking tumors while leaving healthy tissue unharmed.

The key to the drug is actinium-225, a radioactive isotope produced at the Department of Energy's Oak Ridge National Laboratory under the direction of DOE's Isotope Program.

Actinium-225 is an alpha emitter, spewing out tiny bundles of energy that promise to kill cancer cells, but only at short range.

This isotope and others like it are the focus of an exciting new cancer treatment called targeted alpha therapy, which promises eventually to destroy as-yet-untreatable cancers — even those that have spread — while avoiding the side effects associated with chemotherapy and external radiation.



"The beauty of something like an alpha emitter such as actinium-225 is that it's powerful enough to be able to treat the metastatic disease as well as the primary tumor," said Sandra Davern, head of ORNL's Radioisotope Research and Development Section.

The short range of the isotope's effects means the impact on normal tissues beyond the tumor is minimal.

"That's a huge leap forward in how to treat disease, because it's a precision therapy," Davern said.

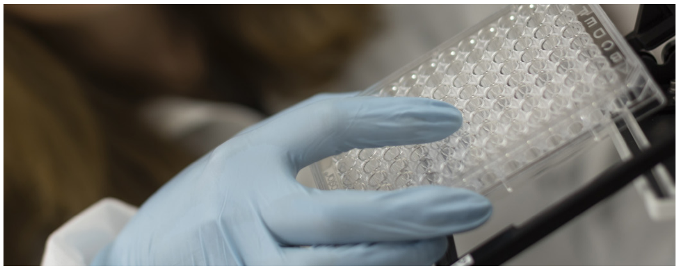
Alpha particles consist of two protons and two neutrons. They are especially promising in the fight against cancer for two reasons: the intense energy they emit and the short distance that energy travels.

In the body, an alpha particle blasts everything within two to 10 cells. Beta particles, consisting of high-energy electrons or positrons, are also used in nuclear medicine, but they radiate 10 times farther while delivering less energy.

Rethinking cancer treatment, one patient at a time

"The promise of targeted alpha therapy is a potentially life-changing cancer treatment using isotopes produced here at ORNL," said Jeremy Busby, ORNL's associate laboratory director for isotope science and enrichment. "This is an outstanding example of the impact the work we do here has out in the real world, on real people."

The therapy is very promising and very much needed. Cancer is America's second leading cause of death (heart disease is first). The country will see more than 2 million new cancer cases this year and more than 600,000 cancer deaths: four new cases and one death every minute.



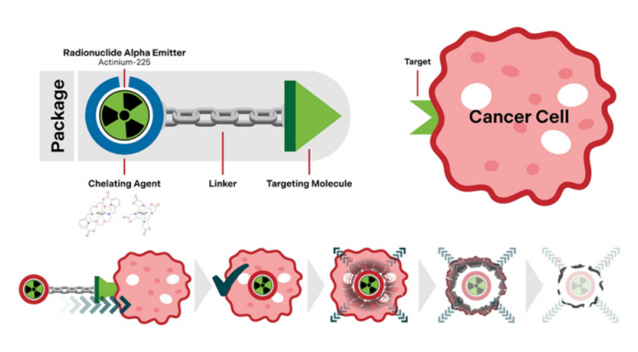
Traditional cancer therapies like chemotherapy (using drugs) and external radiation often come with serious side effects, damaging the heart, lungs, and other organs and causing hair loss, nausea and fatigue. In addition, a cancer may become resistant to traditional treatments, and sometimes a patient's body can't tolerate them.

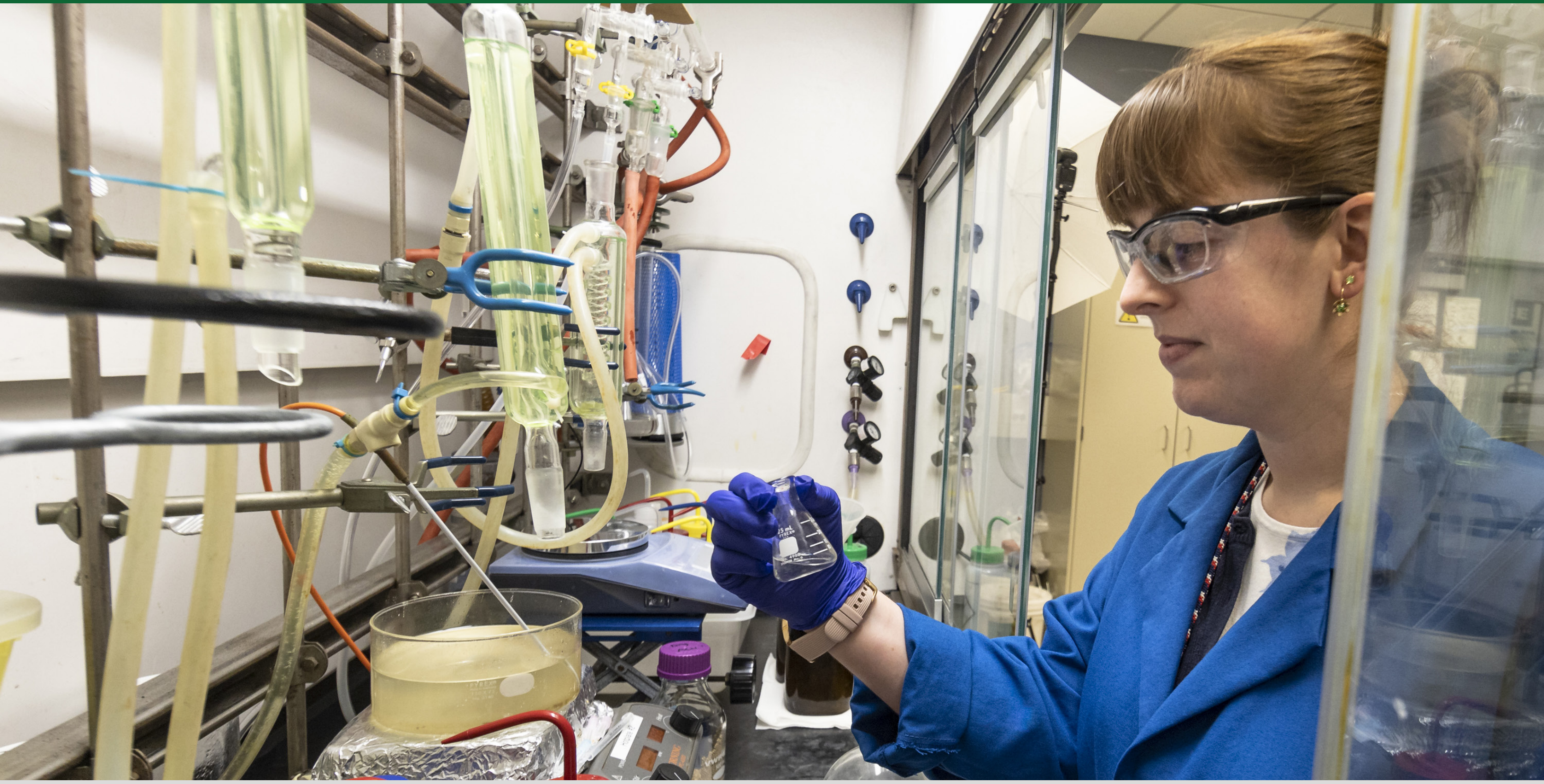
Alpha-emitting radionuclides have potential for treating even the most resistant cancers because they annihilate the cell so that it can't recover, Davern said. Targeted alpha therapy also could avoid the worst side effects.

Packaging targeted alpha therapy

Targeted alpha therapy drugs consist of tiny packages with three components: an alpha emitter (in this case actinium-225), a molecule that seeks out the cancer, and a molecular suitcase holding it all together.

If the package is successful, the actinium-225 and its radioactive daughters will emit five alpha particles in relatively short succession, destroying the cancer cells, or at least the DNA that allows them to reproduce, while leaving healthy, noncancerous cells minimally affected.





ORNL researchers are working on two leading candidates for the molecular suitcase: chelators (pronounced "KEY-laters") and nanoparticles.

Chelators, the smaller of the two, are groups of atoms that hold onto metals, including medical radioisotopes of actinium, lutetium and radium.

But chelator development hasn't kept pace with the arsenal of emerging new radioisotopes.

"We went from one chelator 10 years ago to a dozen chelators that are able to bind and stabilize actinium-225," said ORNL chemist Nikki Thiele. "But for other radioisotopes, we still lack chelators that can deliver them to cancer cells."

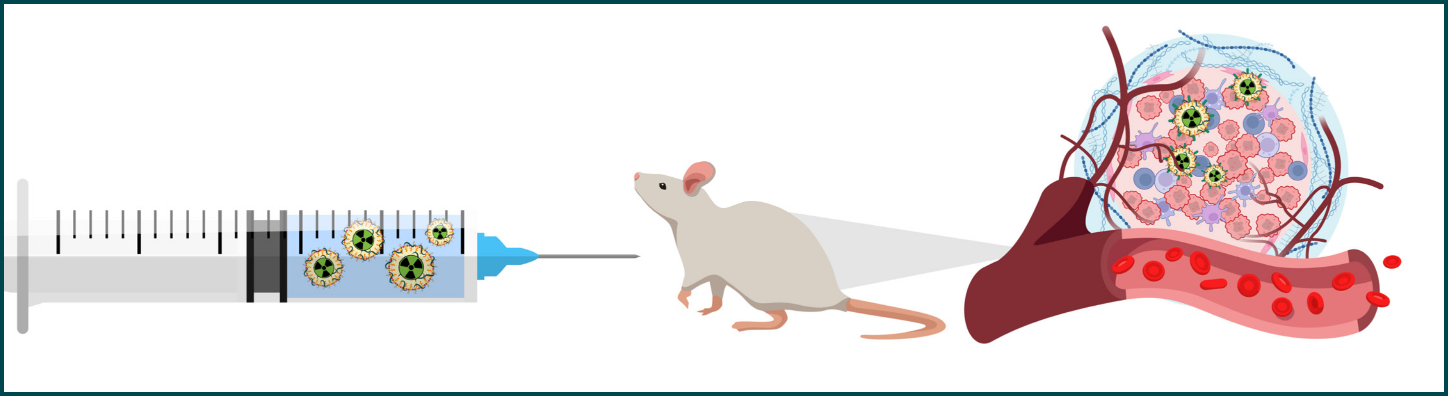
A potential drawback in using chelators for targeted alpha therapy is that they can't keep the package together long enough.

When an alpha emitter ejects the first alpha particle, it produces a recoil, Thiele explained. "The energy released when the alpha particle is emitted exceeds the energy of 10,000 chemical bonds, so release of the alpha particle will break apart the chelator from the daughter radioisotope."

One solution, she said, is to use targeting vectors that take the package inside cancer cells, so that the cells themselves corral the decaying radioisotopes as they release alpha particles.

"Once it is pulled into a cell, it won't really matter if the package falls apart," Thiele said. "If the daughter radioisotopes are released in the cell, they're unlikely to come back out."

A new delivery system for alpha therapy: nanoparticles



Another packaging system employs tiny, often hollow particles known as nanoparticles to enfold the radioisotope while it travels to a tumor.

Nanoparticles are at most 100 nanometers across, roughly one-thousandth the width of a human hair.

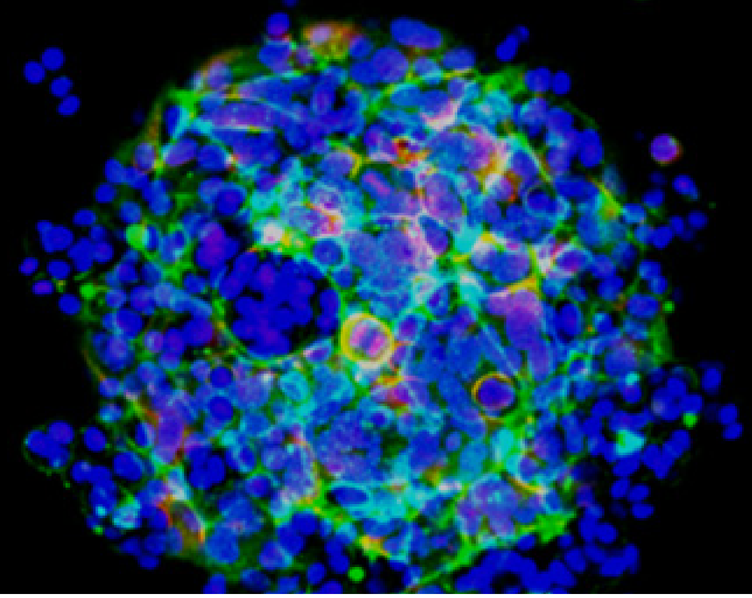
They're a diverse bunch. They can be made up of organic materials such as polymers and lipids or inorganic materials such as metals, and they can take a variety of shapes.

And what they do best is hold tiny packages.

"Certain nanoparticles, especially hollow types, allow encapsulation of actinium-225 or drugs," said ORNL cancer researcher Debjani Pal.

Although researchers are just beginning to study nanoparticles for targeted alpha therapy, they have been used to deliver chemotherapy drugs for three decades.

Besides being able to hold onto radioisotopes while they emit alpha particles, nanoparticles can deliver larger payloads than chelators," Pal said. Where a chelator often can hold only one radioisotope, a nanoparticle can carry many particles and massively increase the dose to the tumor site.



Many directions for targeted alpha therapy research

Davern and colleagues have many challenges ahead: dealing with cancer cells that are not wiped out by treatment; protecting the liver and kidneys, through which the radioisotopes travel to exit the body; attacking cancers for which there are no current targeting vectors.

"In addition to studying better ways to deploy the radioisotope," Davern said, "researchers are looking at what happens at the edges of the treatment range. If alpha therapy kills everything within 10 cells, what happens to the eleventh or twelfth? You want to believe treatment will kill all the cancer cells, but the history of cancer treatments would suggest caution."

"All of the treatments, when they were first rolled out, everyone thought, 'Oh, this is it. This is the cure,'" Davern said. "And sometimes it was the cure … for five years. Or it was the cure for 10 years. But then disease arose elsewhere in the body."

For targeting vectors, Davern's collaborators are focusing on ovarian and breast cancers, for which good targets are lacking.

"What's available on the market right now mostly targets prostate cancer, and so we felt this was a niche that we could go after that was slightly different," she said.

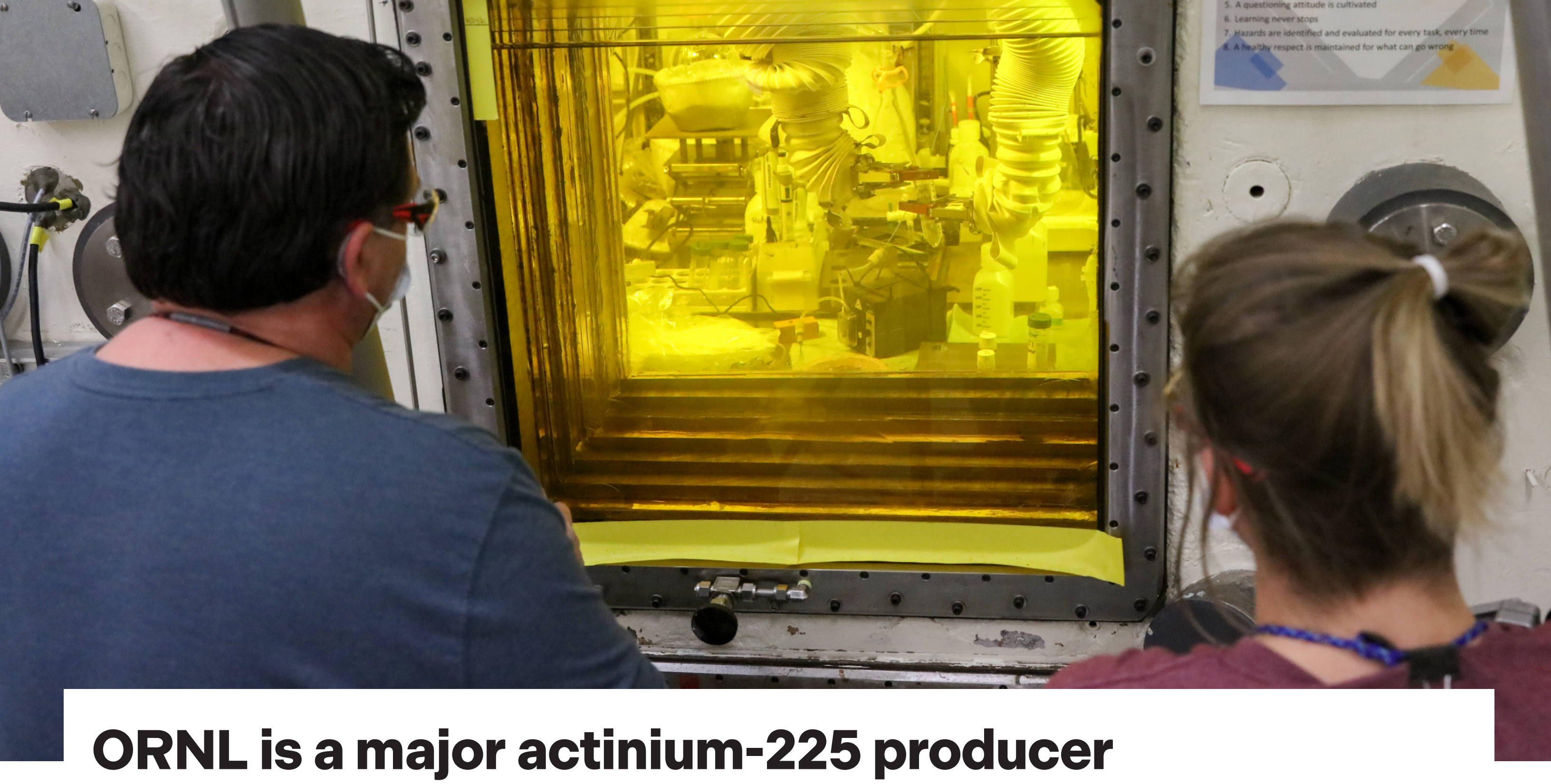
Broadening the search for radioisotopes

In addition to actinium-225, Davern noted that ORNL researchers are working with two isotopes of radium: radium-224, for which the medical isotope lead-212 is a daughter, and radium-223.

There are many reasons to work with multiple alpha emitters, Davern said, from supply chain uncertainties to the varying characteristics of different tumors.

"Depending on the type of tumor, you may benefit more from a shorter-lived radioisotope. So, actinium-225 has a 10-day half-life. But the radium/lead half-life is shorter."

The potential for drug resistance is another reason to hedge their bets, she noted. Conventional wisdom holds that drug resistance won't be a problem for targeted alpha therapy, but conventional wisdom has been wrong in the past.



ORNL is a major actinium-225 producer

But actinium-225 is the first best hope for targeted alpha therapy, and ORNL is one of its few producers. The government's database of clinical research studies lists more than 40 studies that use the radioisotope. They focus on a wide variety of cancers, including those affecting the prostate, liver and lungs, leukemia, and cancers that have metastasized.

Most radioisotopes produced at ORNL come from the lab's High Flux Isotope Reactor, a DOE Office of Science user facility, but actinium-225 is an exception. It is a triumph of recycling, produced primarily from nuclear waste, specifically uranium-233 previously enriched as a possible reactor fuel. Uranium-233 decays to thorium-229, which decays to radium-225, which then decays to actinium-225. ORNL keeps a supply of thorium-229 to process and purify the actinium-225 decay product.

"What's really cool about it is for decades we've had this nuclear waste lying around that is subject to all of the nuclear material accountability control processes," said Ryan Culler, ORNL's program manager for actinium.

"Well, it turns out it's very valuable in the sense that it decays into thorium-229, which is really, really useful."

Making it available for drug development

To get actinium-225 to patients, the lab must meet a stringent set of quality regulations established by the Food and Drug Administration. The job of communicating the manufacturing process to the FDA falls largely to ORNL's Jamie Singer, a regulatory affairs specialist who has worked in drug development for 30 years.

Once ORNL has produced actinium-225 from thorium-229, under DOE authority and guidance, ORNL ships the radioisotopes to drug companies or clinical trial sponsors at universities, whose experts incorporate them into their therapies, Singer said.

Meeting the challenge of getting life-saving radioisotopes to patients

Shipping radioisotopes has always been a unique challenge, but with ORNL production reaching all-time highs, the pressure has never been greater. To meet the goals of DOE, the lab is focused on providing a reliable U.S.-based supply that ensures that American clinical trials can proceed without interruption, supporting patients and advancing U.S. medical innovation.

"If we miss a delivery — if we miss providing a dose to a customer — then that means a patient in a clinical trial misses their dose," Culler said, "which could put that entire trial in jeopardy. It is also heart-breaking for the patient; this is often their last chance at getting more time."

Increasing the production of actinium-225

Uranium-233 is not an unlimited resource. ORNL possesses much of the world's current supply, but private companies are procuring the isotope and preparing to start routine production. The process of producing actinium-225 from uranium-233 requires shielded hot cell facilities and is possible at only a handful of other organizations. If drugs using the radioisotope are approved by the FDA, much more of it will be needed.

DOE has another method for producing actinium-225 — using proton accelerators at Los Alamos and Brookhaven national laboratories to irradiate thorium-232 targets and then purifying the resulting actinium at ORNL and Brookhaven.

"There's multiple private industries that are investing heavily in actinium," Culler said, "because everyone sees the potential. So, if we can get the drugs approved by the FDA through the clinical trials, it may be easier for industry to begin to meet the supply demand."

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