ONCOLOGY

Targeted radioactive drugs raise hopes for treating cancer

Radioconjugates hitch known radioactive isotopes to tumor-targeting tails. Scientists think they might change cancer care

by ***Leigh Krietsch Boerner***

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Credit: Yang H. Ku/C&EN/Shutterstock

Peter Boerner ran out of cancer treatments in the spring of 2015. Up to that point, he had tried pretty much every option, including surgery when he was first diagnosed with stage 3 prostate cancer in August 1993 and radiation therapy that spring.

Boerner responded well to most of the medications—at first. But the cancer kept coming back, popping up in new places in a malignant game of whack-a-mole. “He’d take different medications,” says his wife, Nancy Boerner, “and these would be effective for a bit. Then we’d try another. The effective period would be shorter and shorter, until they just . . . stopped working.”

The cancer spread to Boerner’s bones, including his skull. A tumor pressed into his brain, causing him pain and trouble seeing. As a last resort, he tried external-beam radiation, concentrating on his head. But the treatment ended up being debilitating. He could barely move for days afterward, Nancy Boerner says. So they gave up.

In early 2015, Boerner got a new granddaughter, whom he met only a handful of times. Boerner was too weak for many visits or even to hold the baby on his own. “I love you,” he’d whisper to her, over and over again. “I love you.”

Boerner died in June of that year at age 89. He was my father-in-law, and that baby is my daughter, now 7 years old. She doesn’t remember him.

IN BRIEF

We may never have a cure for cancer, but a new type of drug, called radioconjugates, is grabbing the attention of oncologists. Like external radiation therapy, these drugs use radiation to kill tumors, but they do it internally with the help of cancer-seeking guides. Biotech firms are springing up to study and develop radioconjugates, joining big companies like AstraZeneca, Bayer, and Novartis. The US Food and Drug Administration has already approved two radioconjugate drugs: Lutathera and Pluvicto. Scientists have more work to do to design these drugs and make them targetable while finding and sourcing the right radioisotopes. Still, many see this new class of molecules as a promising part of future cancer treatments.

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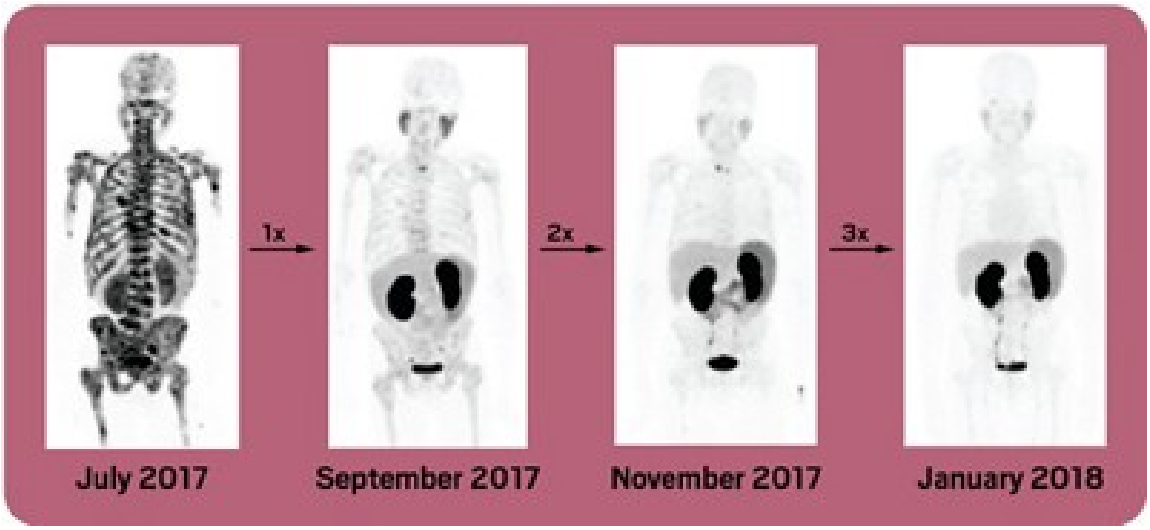
The story of my father-in-law's death is personal, but it's not unique. Almost 10 million people worldwide die of cancer every year, so millions of families have a story like mine.



Credit: *Eur. J. Nucl. Med. Mol. Imaging*/Yang H. Ku/C&EN

In a pilot study, three treatments of an actinium-225 radioconjugate over 6 months cleared up a patient's metastasized prostate cancer (black spots).

Cancer is the second biggest killer in the world, responsible for 1 out of every 6 deaths in 2020, according to the **World Health Organization**. There is no cure for the disease, and there may never be one. Now a new type of treatment is grabbing attention and raising hopes in the oncology community. Called radioconjugates, these drugs combine a radioactive isotope with a targeting agent that seeks cancer cells.

"The treatment is amazing for many patients," says Steffen Schuster, CEO of ITM **Isotope Technologies Munich**, a biotech company that has been working on radioconjugate drugs for various types of cancer since 2009. It's just one of many companies, big and small, getting into the development of radioconjugates.

Peter Scott, an expert on nuclear medicine and a medicinal and organic chemist at the University of Michigan, explains the buzz with an image from a 2019 paper showing a radioconjugate pilot treatment in a person with advanced metastasized prostate cancer. This now well-known image shows a series of positron-emission tomography/computed tomography (PET/CT) whole-body scans of the person—one before treatment and the others after each of three cycles of treatment (*Eur J. Nucl. Med. Mol. Imaging* 2019, DOI: **10.1007/s00259-018-4167-0**). "This patient has metastatic prostate cancer to the bone, more or less everywhere," Scott says. By the end, the radioconjugate has basically cleared up the cancer.

In the past 5 years, biotech start-ups researching radioconjugates have been springing up like mushrooms. Big companies, including AstraZeneca, Bayer, and Novartis, are also getting into the game, on their own and in partnerships with some of these smaller companies, such as ITM and **Fusion Pharmaceuticals**.

"Historically, pharma's been gun shy when it comes to radiotherapeutics," Scott says. But then along came Bayer. In 2013, the US Food and Drug Administration approved the company's drug Xofigo, which is not a radioconjugate but a straight radium-223 dichloride therapy for prostate cancer. Bayer showed the Big Pharma world that internally administered radioactive cancer treatments could be successful, Scott says.

This success may have spurred **Novartis to buy Advanced Accelerator Applications** for $3.9 billion in 2018 and go on to acquire Endocyte for $2.1 billion. That deal included a lutetium-177-based prostate cancer drug, then in Phase 3 clinical trials.

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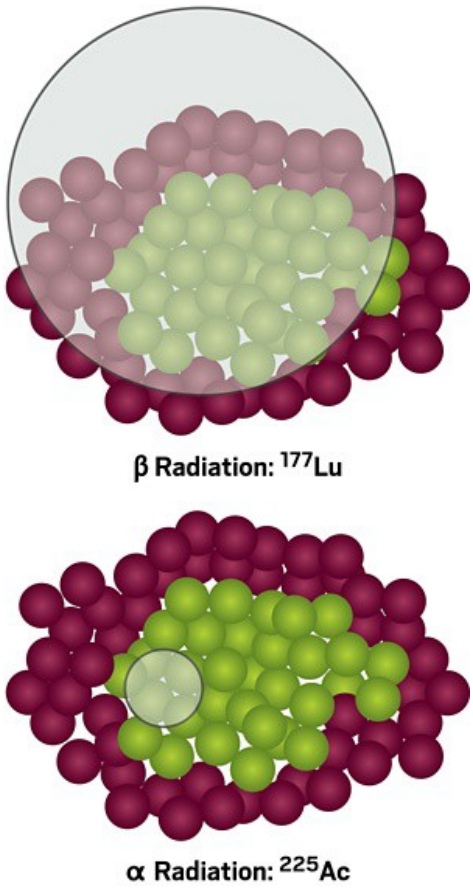
Since then, the FDA has approved two radioconjugate drugs. In 2018, Novartis gained approval for the neuroendocrine cancer drug Lutathera, a radioactive ^{177}Lu compound developed by Advanced Accelerator Applications.

And in late March 2022, the FDA cleared the ^{177}Lu drug Novartis gained from Endocyte, **Pluvicto**. This therapy treats the type of cancer my father-in-law had, metastatic castration-resistant prostate cancer. “Novartis made a bet,” says Andrew Cavey, the global program head for prostate cancer at Advanced Accelerator Applications. There was some anecdotal evidence that radioconjugates worked against prostate cancer, and the data have borne out their effectiveness, he says.

Developing radioconjugates presents many obstacles. The drugs need to be carefully programmed to target the tumor, the type of radioisotope must be chosen carefully, and issues with supplying the radioactive components need to be ironed out. Even so, scientists are confident that the future of cancer treatment lies at least in part in radioconjugates. “I can see a future where we start to develop more [radioisotopes] for cancers that still currently can’t be treated,” Scott says.



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In β radiation (top), particles travel about 2 mm, or 75 cell lengths, from the isotope source, while in α radiation (bottom), particles travel only about 80 μm, or 2 cell diameters. Therefore, β emitters can treat a greater area (shown in the large circle), but are more likely to damage healthy cells (purple). α Emitters reach fewer cells (shown in the small circle) but are more prone to killing only cancer cells (green).

RADIOCONJUGATE RECIPE

Radioconjugates are made of four parts: a radioactive isotope, a chelating agent, a linker, and a targeting molecule. Scientists choose the targeting molecule such that it binds specifically to an antigen that’s highly expressed in cancer cells.

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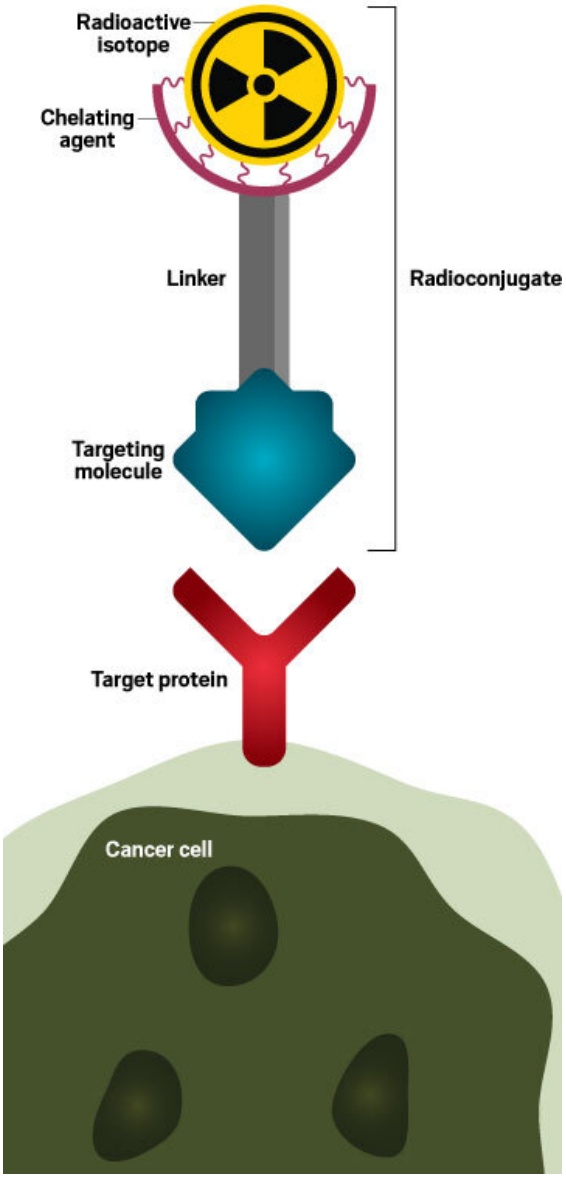

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Source: Adapted from the National Cancer Institute.

THINK GLOBALLY; ACT LOCALLY

There are many ways to treat cancer, but many of them can make patients very sick. “Chemotherapy is a pretty brutal method of treating cancers,” says **Chris Orvig**, a medicinal inorganic chemist at the University of British Columbia who does radiopharmaceutical chemistry. This is because chemotherapy doesn’t discriminate—it kills healthy cells as well as cancer cells. “You’re basically poisoning the entire patient, but the cancer is a little more susceptible. So you’re poisoning the cancer a little more,” Orvig says.

Radiation is also an anticancer tool, killing cells by damaging their DNA. One common type is external-beam radiotherapy, the treatment my father-in-law tried shortly before he died. In this technique, doctors aim and fire photons at a specific area of a patient. The method is more targeted than chemotherapy, but it can also kill healthy cells.

“You’re shooting everything in the area,” Orvig says, which “means you’re going to radiate lots of healthy tissue.” And the external-beam method isn’t effective on cancers that have metastasized throughout the body, says **Puja Sapra**, senior vice president of biologics engineering and tumor-

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targeted delivery at AstraZeneca.

Antibody-drug conjugates, which use a cancer-specific antibody to deliver a chemotherapeutic agent to a tumor, are even more targeted, and a **few have reached the market**. But as with other cancer treatments, cancer cells can gain resistance to antibody-drug conjugates, rendering them less effective after a while.

With radioconjugates, drug companies are using the same conjugate approach, but instead of delivering a toxic molecule, the therapy delivers a cancer-killing isotope.

"Essentially, it's like an arrow where the receptor-targeting ligand, or the feathers, get it there, and the damage is done by the arrowhead, which is the radioactive isotope," Orvig says. The targeting end is designed to bind specifically to an antigen that's expressed more highly in cancer cells. "Here the hope is to use a targeting molecule to deliver radiation precisely to tumor cells and avoid the normal, healthy cells," Sapra says. Unlike external radiation, she says, radioconjugates can dispatch radiation to multiple tumors at the same time.

Another advantage of radioconjugates is that the mechanism of action is relatively straightforward, says Alonso Ricardo, chief scientific officer of **Curie Therapeutics**, a biotech firm developing targeted cancer radiotherapies.

"You're talking about something that is getting inside the cell and destroying the DNA," Ricardo says. Unlike antibody-drug conjugates, radioconjugates do not have to restrict a key biological pathway or inhibit some mechanism, so cells are unlikely to evolve a biological workaround to avoid the radioactive damage, he says.

Companies that are working on radioconjugates generally have their sights on two types of isotopes: α emitters and β emitters. Each has advantages and disadvantages.

α **Emitters** give off a particle, called an α particle, made up of two protons and two neutrons—essentially a helium atom minus its electrons. Compared with β particles, "they're heavier; they don't travel as far," Orvig says, only about two cell diameters from the radioisotope, making the radiation less likely to hit nearby healthy cells. α Particles have higher energy than β particles and cleave both of DNA's strands. "If you could target that to a cancer, you could do a lot of damage to the cancer and hopefully not much damage to the surrounding tissue," he says.

Actinium-225 is a popular α emitter because it's an α generator, Ricardo says. It doesn't give off just one α particle but starts a cascade chain in which multiple α emitters form. "Every molecule of ^{225}Ac is going to start decaying and shoot four α particles," Ricardo says. The chain eventually stops at the stable isotope bismuth-209.

The two FDA-approved radioconjugates, Lutathera and Pluvicto, use β emitters. These eject β particles, essentially electrons, which have a lower energy than α particles but travel farther in the body, about 2 mm, or 75 cell diameters, ITM's Schuster says. They cleave only one of DNA's double strands.

Which emitter is best to deploy depends on the type of cancer and the target. For example, neuroendocrine tumors grow slowly, Schuster says. "In this case, we would go with β emitters. If you take ovarian cancer, for example, it's a very aggressive cancer type, and in this case, the α emitters are probably the better choice." But the choice will vary case by case, he says.

Both types of emitters have a place in cancer treatment, AstraZeneca's Sapra says. Hypothetically, doctors could start treatment with one type of emitter and then switch to the other if a resistance mechanism emerges, she says. "It's not a bad strategy to have both in your arsenal."

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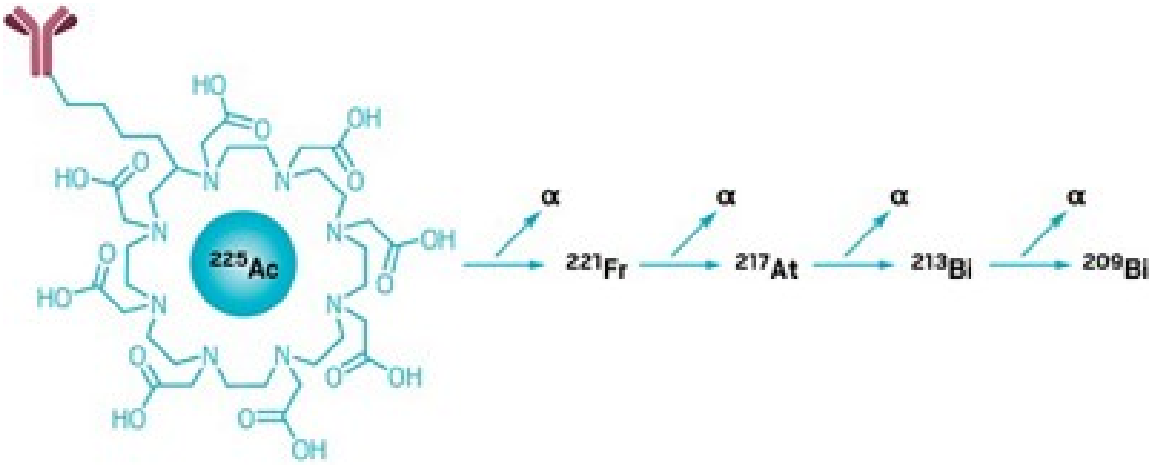
> — ***Puja Sapra**, senior vice president of biologics engineering and tumor-targeted delivery, AstraZeneca*

Another powerful aspect of radioconjugates is that they can do dual duty: scientists can insert an imaging radioisotope into the conjugate to track cancerous cells, then swap in a tumor-killing isotope to destroy them. “You have the same targeting molecule, the same linker that you use to connect the isotope, but you replace your therapeutic isotope with a diagnostic isotope. It’s effectively the same drug,” says John Valliant, CEO of Fusion.



Actinium-225 is an α generator, which gives rise to a chain of reactions, each emitting one α particle. A radioconjugate molecule containing ^{225}Ac (left) can deliver four α particles by the time it decays to bismuth-209, a stable isotope.

Other types of radioisotopes, such as positron and γ emitters, are often used as imaging agents. Gallium-68 and indium-111, for example, are easily picked up via PET/CT scanners, allowing doctors to see where the radioconjugates go in a patient’s body and therefore what areas have cancer cells. “In our clinical trials, every patient gets imaged,” Valliant says. “And if they show the appropriate uptake of the drug, they then go on and get the therapeutic form of the drug.”

Or as Schuster puts it, “You see what you treat, and you treat what you see.”

With most other cancer treatments, patients have to go through several rounds of treatment before doctors can do an imaging study to see if the cancer is retreating. “You’re just waiting to see if you had a response,” Ricardo says.

PUTTING THE PIECES TOGETHER

The chemists researching radioconjugates love their analogies, describing the basic structure of the compounds as arrows, missiles with warheads, or baseballs in mitts. Whatever the metaphor, the conjugate has to have the same four basic components: the radioactive isotope, a chelator to hang on to the isotope, a targeting compound, and a linker to hold the parts together.

The radioisotopes are toxic, which is the point of anticancer drugs. But this is also a problem, the University of Michigan’s Scott says. “You want [the radioactive metal] to go to the tumor and then stay there. You don’t want that metal ion coming out all over the body and doing damage to anything besides the tumor,” he says.

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This is where the chelating agent comes in. It holds the radioactive ion in a protective basket and connects it to the rest of the molecule via a linker. But it's hard for chemists to design a chelator that doesn't disturb the radioconjugate's overall function. "If you suddenly add a chelating group and it takes away the affinity of the targeting moiety for the target, it's not going to work," Scott says.

Another issue to consider in a chelating agent is the sheer size of the radioisotopes. The metals that scientists often want to use, ^{225}Ac and ^{177}Lu, are inner transition metals, behemoths lurking at the bottom of the periodic table. Big ions need lots of binding atoms, Orvig says, as many as 8–12.

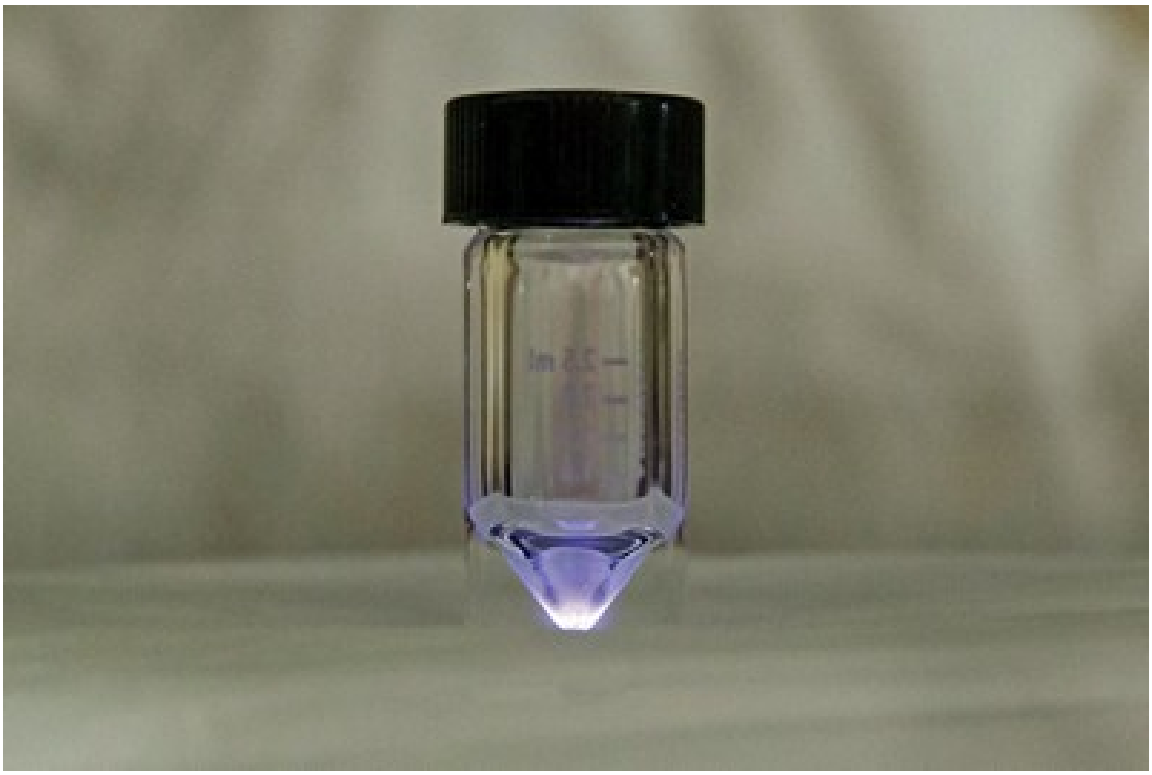
Chemists also need to design a place on the chelator where they can attach the linker, which connects the radioisotope to the targeting group. Many chemists hang groups such as amines and carboxylic acids off the chelator backbone, letting them easily add the linker with amide formation or click chemistry.

The linkers need to be stable to conditions inside the body so that the radioactive component doesn't fall off and go floating away in the bloodstream. At the same time, the linker must break down once the drug has dumped its radioactive energy into tumor cells so that the body can excrete it. "You want the material that's in the tumor to stay in the tumor, and you want the material that's elsewhere in the body to be cleared as quickly as you can," Fusion's Valliant says.

The targeting compound can be as big as a whole protein or as small as a peptide, Curie's Ricardo says. But it has to be something that seeks out receptors that are unique to cancer cells.

And when they put all the parts of the radioconjugate together, scientists also have to think about speed. ^{225}Ac has a half-life of 9.92 days, while ^{177}Lu has one of 6.65 days. This means that once the isotope is attached, companies have to get the drugs to hospitals and treatment centers quickly, while they're still potent.

"You want to design and synthesize a system so that the isotope can basically be added to a vial," Orvig says. He calls such a system "shake and shoot."



Credit: Andrew R Burgoyne, Oak Ridge National Laboratory

Actinium-225 nitrate in a vial glows blue because of the ionization of air by α particles.

TIME TO SHINE

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The field of radioconjugates is poised for rapid development, AstraZeneca's Sapra says. It's aided by years of research into both radiolabeled cancer treatments such as Xofigo and targeted treatments such as antibody-drug conjugates. "There has been so much learning of how to put these pieces together to make an effective conjugate, and combining these learnings with evidence of clinical activity gives us the confidence that the field is at an inflection point," she says.

Along with this burgeoning knowledge, the supply of isotopes for researching and producing radioconjugates is growing after years of lean supply. "For a very long time, we did not have the right radioisotopes," ITM's Schuster says.

> "You see what you treat, and you treat what you see.
>
> — ***Steffen Schuster**, CEO, ITM Isotope Technologies Munich*

Medical radioactive isotopes are not a garden-variety commodity. They can be sourced only from generators, cyclotrons, nuclear reactors, or **old radioactive waste**. Securing the radioisotope supply chain so that scientists can fully realize the power of radioconjugates is going to be key as this field starts to really grow, Scott says.

"But there are several initiatives which are underway at the government level and pharma companies that we believe will get us to the stage that this is more widely available," Sapra says. Some of the producers of radioactive isotopes include Canada's particle accelerator center, **Triumf**; the nuclear innovation company **TerraPower**, founded by Bill Gates; and an **initiative from Oak Ridge National Laboratory** in the US.

ITM makes high-purity ^{225}Ac and ^{177}Lu, for both internal use and selling to other companies. The biotech was founded in 2004 and at first concentrated on finding a reliable way to make needed radioisotopes. It wasn't until 2009 that scientists at ITM started their own drug research and development.

"When we founded the company, we already understood the power of radiopharmaceuticals," Schuster says. "But we also figured out that there was not the right quantity and quality of the appropriate radioisotopes there. So this is why we [fixed] this first."

Now ITM sells ^{177}Lu to more than 450 universities and clinics around the world, Schuster says. Through a partnership with Novartis, the company is supplying ^{177}Lu for Pluvicto. "^{177}Lu is going to be the workhorse of radiopharmaceuticals for the next many years," he says. "And the way we see it, [^{177}Lu] will be complemented by ^{225}Ac."

Joining veterans like ITM and Fusion, many small companies, developing α-emitting radiopharmaceuticals in particular, have cropped up in the past few years, including **RayzeBio**, Curie, **Aktis Oncology**, and **Precirix**. The money is there, Orvig says, from venture capital firms and bigger drug companies. Curie, for example, came out of stealth in late 2021 **with $75 million in funding**, while RayzeBio has raised more than $250 million since its founding in 2020. Venture capital investors just gave Precirix **$88 million** in series B funding in March.

And the opportunities for the new batch of companies are there too, AstraZeneca's Sapra says. "If you think about it, 50% of patients receive and respond to traditional radiotherapy at some point in their cancer journey," she says. "So if we can really deliver it precisely, we can pretty much go after many tumor types."

In addition, there's potential to combine targeted radiation cancer treatment with medicines that already exist. "The primary mechanism of tumor killing by radioconjugates is through direct DNA damage," Sapra says. In the future, doctors could combine radioconjugates with drugs that inhibit DNA damage-repair machinery in cancer cells, she says.

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Schuster expresses great regret when I tell him about my father-in-law. ITM was in early stages of developing radioconjugates in 2015, the year Boerner died, and he may have been able to try the drugs if he had been able to travel to Europe, Schuster says. He knows that no single cancer therapy is a magic bullet. But Schuster says he's seen patients before and after radioconjugate therapy. "I believe strongly that it makes a big difference," he says.

CORRECTION:

This story was updated on April 25, 2022, to correct the description of indium-111. It is a γ emitter, not a positron emitter.

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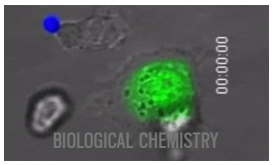

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