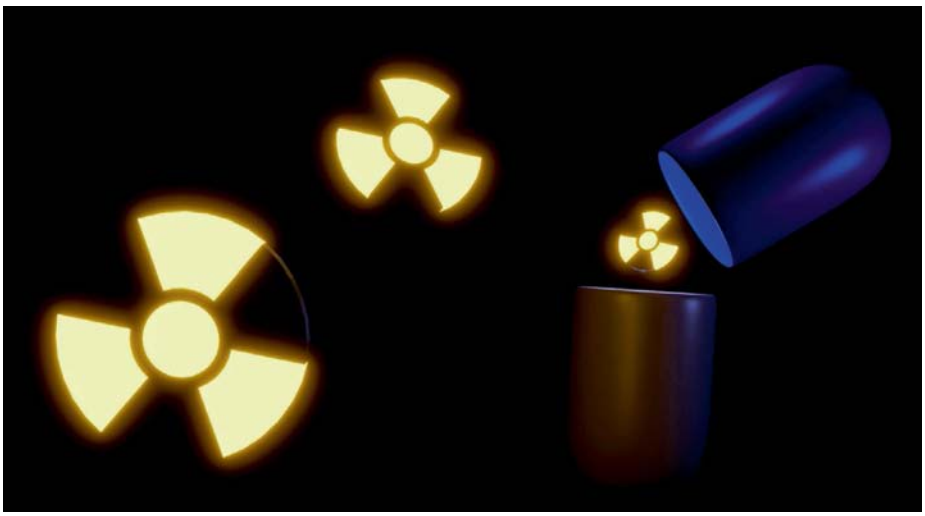
Biopharma dives into tumor-seeking radioactive drugs

Big pharma and investors are piling into the precision radiation space as the next generation of increasingly potent targeted α-particle therapies promises to destroy cancerous cells with minimum damage to healthy tissues.



Radioactive medicines are undergoing a surge in popularity.

By Charlotte Harrison

AdvanCell in February raised $112 million to trial a potentially best-in-class targeted α-radiation therapy for a prostate cancer. The Sydney Australia-based company's radionuclide treatment ADVC001 is in phase 1/2 trials for metastatic prostate cancer. The series C financing injection is yet another sign of growing interest in radiopharmaceuticals that, over the last two years, has led to a string of deals amounting to $10 billion from players such as Novartis, Eli Lilly, AstraZeneca and Bristol Myers Squibb. These four big pharma are betting on a new and more potent radioisotope than what has been used in US Food and Drug Administration (FDA)-approved drugs so far. The newer α-emitting isotope therapies are poised to make a splash in oncology because they deliver focused radiation directly to cancer cells. For patients, it could "change the paradigm of cancer care," says Arnaud Lesegretain, CEO of Orano Med.

Radiopharmaceutical drugs are small molecules, peptides or antibodies hooked via a linker to a radioactive payload. These therapies containing radioactivity deliver radiation directly to tumor cells, damaging the cells' DNA and causing cell death while sparing surrounding healthy tissues.

The best-selling radionuclide therapeutic is Novartis's Pluvicto (lutetium Lu-177 vipivotide tetraxetan), approved by the US FDA in 2022 for metastatic prostate cancer. Pluvicto uses the isotope lutetium-177, a β-emitter that releases high-energy electrons to cause single-stranded nicks in DNA, targeted to the prostate-specific membrane antigen (PSMA) found on prostate tumor cells. The other approved radiotherapy, Norvartis's Lutathera (lutetium Lu-177 dotatate), uses the same β-emitting lutetium-177 but targets it to somatostatin receptor type 2 (SSTR2) to treat neuroendocrine tumors.

Newcomer radionuclide agents carry a different type of isotope: α-emitters. They boast some key advantages — they dispatch more DNA damage at closer range — leading drug developers to turn increasingly to lead-212, astatine-211 and actinium-225. An α-emitting radionuclide throws off a helium nucleus — an α particle — which, though more potent in energy transfer, penetrates only a few cell layers. This results in irreparable double-strand DNA breaks only in the targeted cancer cells while limiting collateral damage to nearby healthy cells. The alluring prospect is that this short-range damage can be specifically focused on tumor cells by combining α-emitters with biological molecules. Trials testing such molecules on neuroendocrine tumors are beginning to read out, and results so far "look extremely exciting," says Ebrahim Delpassand, CEO of RadioMedix. Those results include those for RadioMedix's candidate AlphaMedix, licensed to Sanofi, which delivers lead-212 to SSTR2. It shrank advanced neuroendocrine tumors in around 55% patients, with no evidence of disease in many patients.

Drugmakers now aim to extend this success to other types of cancer. "The menu on these drugs will increase," says Delpassand. "And, in the future, we'll be able to attack cancers that, at this point, we don't have good therapy for," he says. One of those hard-to-treat cancers that researchers are hopeful about is high-grade glioma, an infiltrative and immunosuppressive brain cancer. Companies are using targets such as the low-density lipoprotein receptor, carbonic anhydrase XII or L-type amino acid transporters, typically overexpressed in gliomas. Trials are at early stages (Table 1), but results could come quickly because isotopes directed at a certain target can also allow tumors to be visualized before and during therapy, an approach known as theranostics. The imaging, using a weakly radioactive isotope, allows clinicians to visualize patients' lesions for target expression, to select them for trial and to track the agent's uptake to manage dosing of the therapy.

Radionuclide therapies might even step in where other targeted anticancer drugs reach their cap. Antibody–drug conjugates (ADCs), for instance, are hugely efficacious but are limited by unacceptable toxicity profiles. By contrast, precision radiation may prosecute low-expression targets that ADCs, with their limited payload, cannot tackle. Even for cancers with low-expression targets, the α-radiation is powerful enough to destroy them. In manufacturing, it is also possible to ramp up radiopharmaceuticals' activity by adding more

News in brief

Consternation follows Marks' FDA departure

In late March, the US Food and Drug Administration's (FDA) director of the Center for Biologics Evaluation and Research, Peter Marks, resigned under pressure from Health and Human Services Secretary Robert F. Kennedy. In his resignation letter Marks said he had been asked to hand in data on measles vaccine-related deaths and brain swelling that do not exist.

Marks' resignation corresponds with a massive government cull from across Health and Human Services seeking to eliminate at least 3,500 jobs from the FDA, 2,400 from the Centers for Disease Control and Prevention and 1,200 from the National Institutes of Health. With many of the top jobs at the FDA vacant as a result of layoffs, resignations and a hiring freeze, public and industry leaders are sounding the alarm. David Kessler, a former FDA commissioner, warns, "If these cuts are not rescinded, they will have an effect for decades."

Jeremy Levin, Ovid CEO, is among over 200 industry leaders, investors and patient advocates who penned a letter to US Senate Health, Education, Labor and Pensions committee chairman Bill Cassidy, Republican of Louisiana, raising concerns about the state of the agency: "Specifically, we worry that the institutional knowledge that makes the FDA the world's leading regulatory body will be irretrievably lost." In addition to jobs, the administration has slashed science funding, particularly for programs involving infectious diseases such as HIV and COVID-19 and for vaccines and LGBT-related projects. Nearly 800 research projects have been terminated and by April more than $2.3 billion had been cut.

Table 1 | Selected therapeutic clinical trials of radiopharmaceuticals, excluding PSMA and SSTR2 as targets

Company	Molecule; radiation	Ligand type	target	Stage, indication
Abdera Therapeutics	^{225}Ac-ABD-147; α-emitter	Heavy-chain antibodies	DLL3	Phase 1; lung cancers
Clarity Pharmaceuticals	^{67}Cu-SAR-bombesin; β-emitter	Peptide	GRP-R	Phase 1/2; prostate cancer
Debiopharm	^{177}Lu-DPI-4452; β-emitter	Peptide	CAIX	Phase 1/2; solid tumors
Fusion Pharmaceuticals (part of AstraZeneca)	^{225}Ac-FPI-2059; α-emitter	Peptide	NTSR1	Phase 1; solid tumors
Novartis Pharmaceuticals	^{177}Lu-NeoB; β-emitter	Peptide	GRP-R	Phase 1/2; breast cancer
Novartis Pharmaceuticals	^{177}Lu-FAP-2286; β-emitter	Peptide	FAP	Phase 1/2; solid tumors
Perspective Therapeutics	^{212}Pb-VMT01; α-emitter	Peptide	MC1R	Phase 1/2; melanoma
Point Biopharma (part of Lilly)	^{177}Lu-PNT6555; β-emitter	Peptide	FAP	Phase 1; solid tumors
Radiopharm Theranostics	^{177}Lu-RAD204; β-emitter	Single-domain antibody	PD-L1	Phase 1; solid tumors
Radiopharm Theranostics	^{177}Lu-RAD202; β-emitter	Single-domain antibody	HER2	Phase 1; solid tumors
Telix Pharmaceuticals	^{131}I-TLX101; β-emitter	Amino acid	L-type amino-acid transporters	Phase 1; glioblastoma
Y-mAbs Therapeutics	^{177}Lu-CD38-SADA; β-emitter	Self-assembling antibody	CD38	Phase 1; non-Hodgkin's lymphoma
RayzeBio (part of Bristol Myers Squibb)	^{225}Ac-RYZ801; α-emitter	Peptide	GPC3	Phase 1; hepatocellular carcinoma
ITM Radiopharma	^{177}Lu-ITM-31; β-emitter	Antibody Fab fragment	CA XII	Phase 1; glioblastoma

CA XII, carbonic anhydrase XII; CAIX, carbonic anhydrase IX; CD38, cluster of differentiation 38; DLL3, delta-like ligand 3; FAP, fibroblast activation protein; GPC3, glypican-3; GRP-R, gastrin-releasing peptide receptor; HER2, human epidermal growth factor receptor 2; MC1R, melanocortin 1 receptor; NTSR1, neurotensin receptor 1; PD-L1, programmed death-ligand 1.

radioactivity. And inside the body, their mechanism is simple — they do not need to be taken into the cell to work. "It can help, but it's not a required condition for radiopharmaceuticals to operate," says Orano Med's Lesegretain.

The developers' challenge, however, is to maximize radioactivity onto the tumor and keep it there long enough for the radioisotope to fully deliver its cell-killing damage while ensuring minimal damage to nearby healthy cells. This is still work in progress: "Unfortunately, nobody has cracked the code [for these challenges] across targets," says Daniel Steiner, senior vice president of research and technology at Zurich, Switzerland-based biopharma Molecular Partners.

When it comes to delivering the radioactive payload, peptides are most drugmakers' top choice (Table 1). This popularity is no doubt buoyed by their use in Pluvicto and Lutathera. "Peptides are the perfect delivery system for radionuclides," says Michael Skynner, chief technology officer at Bicycle Therapeutics, noting advantages such as short systemic half-life and rapid clearance through the kidneys. However, the kidneys tend to reabsorb amino acids, so limiting the isotope buildup in this organ is important.

Biopharma companies are embracing peptides in constellation of new structures to refine and potentiate their therapeutic prowess. Bicycle Therapeutics develops synthetic bicyclic peptides as ligands for cancer targets; its lead molecule is in a phase 2/3 trial and consists of a cyclic peptide conjugated to a toxin. Like several other biotechs now entering the radiopharma field, Bicycle has recently capitalized on its experience in ADCs and is now moving to accelerate the radiopharmaceutical candidates in its portfolio.

Another strategy to latch the radionuclide-carrying peptide onto its target and retain it at a tumor site has been devised by researchers from Peking University in China. They deploy a form of click chemistry – reactions that snap two complementary molecules together fast enough and selectively enough to be used in vivo – to target α- and β-radiation to fibroblast activation protein (FAP), a pan-cancer target expressed in a tumor's stroma. The FAP ligand, when covalently bound to its target, had 2.5-fold more uptake and 13-fold better tumor retention in mice than the non-covalent ligand, as well as better antitumor effects. And, in two patients, the covalent ligand imaged more tumor lesions.

Antibodies can also deliver radionuclide cargoes with exquisite specificity. The drawback is that antibodies could hang around in the body for weeks and, when coupled to radioactivity, could be depositing radiation in the bone marrow and causing hemotoxicity. As a result, drugmakers are now increasingly attracted to peptide mimetics that have the binding affinity of antibodies – for example, antibody fragments, DARPins, cyclic peptides and mini-proteins.

Bicycle Therapeutics' cyclic peptides could meet such requisites. They consist of two linear peptides designed to mimic the epitope-binding region of an antibody, constrained and kept in place by a chemical scaffold. They're "the business end of an antibody in a small molecular format," says Skynner. The company is chasing EphA2, a receptor tyrosine kinase. The short circulation half-life, 40–60 minutes, of its bicyclic-based radiopharmaceutical should overcome the uncontrollable bleeding side effects that halted ADCs aimed at this target. Human imaging data to validate EphA2 as a target are anticipated later this year.

Other antibody-mimetic proteins – the designed ankyrin repeat proteins, or DARPins – can be manipulated to recognize a variety of targets while overcoming another of ADC's shortcomings. The cancer target mesothelin, expressed on certain lung cancers and ovarian cancer, for instance, has proven challenging for ADCs because they tend to bind soluble mesothelin that is shed into circulation. Molecular Partners engineers DARPins to bind targets with high specificity and affinity using ankyrin repeats – naturally occurring anchoring protein domains that mediate protein–protein interactions.

One such DARPin in preclinical studies directs radiation to a cell-surface mesothelin – specifically, to a small membrane-proximal region. "That's really difficult for modalities such as cyclic peptides, in terms of sensitivity and specificity, to achieve," says Steiner. The company's radio-DARPins have optimized backbone surfaces to prevent kidney reabsorption and have been engineered to extend circulatory half-life to boost tumor uptake. One DARPin candidate that directs a radionuclide to cell-surface mesothelin is in preclinical studies. Another candidate that targets lead-212 to DLL-3, an inhibitory ligand of the Notch signaling pathway, is expected to start first-in-human studies this year for small cell lung cancer.

Several other companies have engineered antibody functional units to combine the advantages of small peptides – high solubility and tumor penetration – with the exceptional specificity of conventional monoclonal antibodies. One of the first biotechs to generate clinical data is Precirix. The Brussels-based biotech attached the β-emitter iodine-131 to engineered single-domain antibodies or fragments called nanobodies to deliver the radioactive payload to HER2-expressing tumors. Its single-domain antibodies bind the target and stay on the tumor cells for more than 7 days, and unbound radionuclide is cleared rapidly by the kidney within hours. That study provides clinical proof of mechanism. "Single-domain antibodies as a targeting concept, as a platform, work," says Dimitrios Mantzilas, the company's chief technology officer. The study shows that the product is highly specific for HER2 without causing hemotoxicity. The company is now focusing on radiometals to align with industry trends, with its most advanced program targeting an α-emitting radionuclide to FAP.

Other developers see full-length antibodies as having the ideal attributes for targeting cancer with radioactive isotopes. Tagworks' strategy is to harnesses conventional monoclonal antibodies' high affinity, good tumor exposure and low kidney exposure, and once the job is done, it unhooks the antibody from its radioisotope. The company's click-to-release technology uses a cleavable linker to attach the isotope to the targeting molecule. Once the drug is infused into the patient and the antibody engages its target, a tetrazine molecule is injected, which uses click chemistry to release the isotope. That isotope is then cleared quickly from the body. "[We] take care of the detrimental bone marrow exposure ourselves," says Marc Robillard, founder and CSO of Tagworks. The tetrazine trigger molecule is not cell permeant, so it cannot reach antibody–isotope conjugates that have been internalized by tumor cells, ensuring

News in brief

FDA pushes to replace animal testing

The US Food and Drug Administration plans to introduce computational modeling and other innovative methods to replace animal testing in preclinical drug safety studies, according to a roadmap released in April. By encouraging drug sponsors to embrace organ-on-a chip, in silico modeling, organoid and other in vitro assays, the FDA aims to reduce animal testing to the extent that it becomes "the exception rather than the norm" within 3–5 years. The FDA's roadmap builds on the 2022 FDA Modernization Act 2.0, passed by Congress, which removed the requirement for animal testing in biosimilar biologics' applications.

Monoclonal antibodies are at the forefront of the FDA's push for human-relevant safety testing as animal models are poor predictors of human safety for this drug class. In time, other biologics and small molecules will be included in the FDA's plan. Nevertheless, technologies such as organs-on-chips and organoids, often called new alternative methods (NAMs), are not ready to fully replace animal testing just yet. Recapitulating organs is difficult, and NAMs must be validated to demonstrate they can mimic animal toxicity. Roche scientists showed that patient-derived intestinal organoids, for instance, can determine the on-target, off-tumor toxicities of T cell-engaging bispecific antibodies.

Developers are researching NAMs' utility, but it is not known how much NAM data companies use in FDA submissions, as these documents are not made public. To increase NAMs' knowledge base, the FDA is encouraging sponsors to submit NAM data in parallel with animal data. It is also identifying pilot cases in which an animal study might be waived, such as antibody drugs that target human-specific receptors. In such cases, the FDA could allow a sponsor to substitute organ-on-a-chip plus pharmacokinetic modeling studies instead of a transgenic mouse study.

that radioactivity is trapped in the tumor. A first-in-human trial is expected to start later this year, targeting an isotope to the well-validated HER2 target. "We're doing a very new approach here," says Robillard.

Other companies including Y-mAbs, Roche and OncoOne, as well as academic groups, are exploring the opposite route: attaching a radionucleotide only after pre-targeting with an antibody. A patient first receives unlabeled antibody or self-assembling antibody components that latch onto the tumor, and any that do not bind are cleared through the blood. The patient is then injected with a radiotracer, which combines with the bound antibody via click chemistry or bispecific antibody interactions. Any excess is rapid cleared.

"It's inherently sophisticated in vivo radiochemistry," says Brian Zeglis, a radiochemist at the City University of New York, who co-developed a form of this technology while at Memorial Sloan Kettering Cancer Center. "The primary agent not only needs to bind tumor tissue, but also reach back and grab a radionuclide," he says. An imaging trial is testing this strategy, known as pre-targeting, using an antibody to CA19-9 on pancreatic cancer cells. More advanced is Y-mAbs phase 1 trial using self-assembling antibody fragments to deliver lutetium-177 to the non-Hodgkin lymphoma target CD38. Importantly, no evidence of bone marrow toxicity was seen in mouse models. If this strategy works, "it's almost the grail of going to the tumors, not hitting healthy tissues," says Orano Med's Lesegretain. The company is collaborating with Roche on a pre-targeting approach.

Radiopharmaceuticals open up new doors to innovate and try different chemistry strategies that could eventually produce "a Swiss army knife for radiopharmaceutical design," says Angela Casini, a chemist at the Technical University of Munich who researches these approaches as part of the Horizon Europe-funded SMARTdrugs consortium. One strategy deploys supramolecular chemistry, focused on weaker and reversible interactions between molecules, such as hydrogen bonds. Scientists can apply these non-covalent effects to enable two drug fragments, one of which encapsulates a radionucleotide, to stay together in a reversible, non-covalent interaction. It is possible to add more functionalities to such molecular systems, such as multiple radioisotopes or targeting fragments, giving researchers and drugmakers more flexibility to innovate than with traditional protein or small-molecule engineering.

The other advantage to deploying radiopharmaceuticals is that they could be used as low-dose radiation to complement immunotherapies and boost their effectiveness in treating cancers. One trial has found that a single priming dose of Pluvicto combined with the PD1 protein blocker Keytruda (pembrolizumab) shrank tumors in patients with metastatic prostate cancer. Tweaking radionuclide therapies to lower the radiation dose when combined with immuno-oncology drugs may be particularly effective for childhood cancers, as minimizing radiation dose and exposure is important for young patients.

Researchers from the University of Pittsburgh are testing this strategy in a mouse model of glioma, a cancer that accounts for about one-fourth of childhood cancers. They showed that that 1/50th of the typical dose of α- or β radiation directed to CD11b on tumor-associated myeloid cells sensitized tumors to an immune checkpoint inhibitor. This resulted in a much higher survival rate than treatment with the checkpoint inhibitor alone. "We're working on translating our data and looking at potentially doing clinical trials," says Pittsburgh's Jessie Nedrow, who jointly led the work. The mechanisms underlying low-dose radiation's effect are uncertain, yet radiation-induced damage to tumor cells is likely to exert an immunostimulatory effect on the tumor microenvironment, recruiting immune cells to enhance anti-tumor immunity.

The rapid and massive investment in the radiopharmaceutical arena will undoubtedly drive further understanding and foster further innovation. But some caution against rushing to select ligands or targets that, should they ultimately fail, may end up "tarnishing the trust in the radiopharmaceutical field," said Delpassand. Nevertheless, "Lutathera and Pluvicto could just be the vanguard," says Zeglis. Now that the eyes of physicians, venture capitalists and biotech are on the radiopharmaceutical field, "We can really continue with this momentum," he says.

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