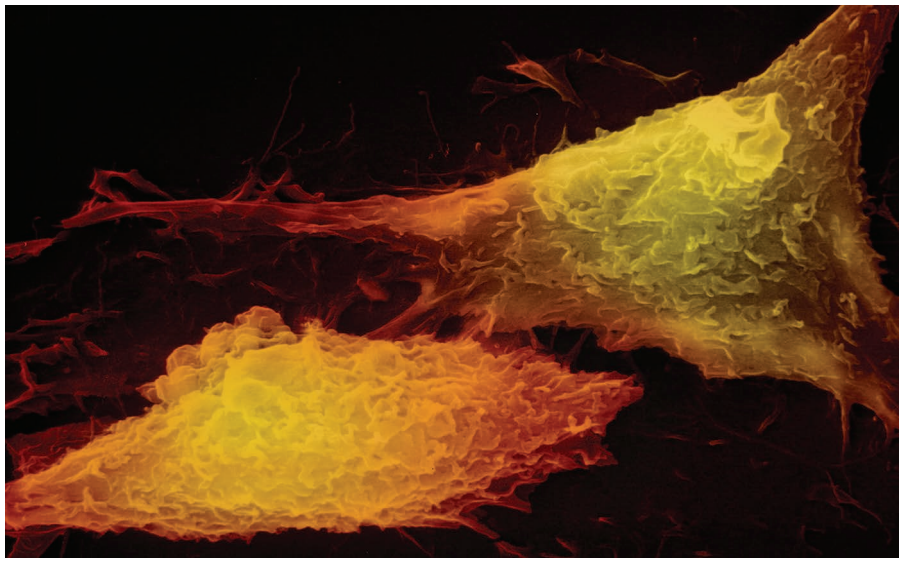
Radioactive drugs emerge from the shadows to storm the market

Novartis is expanding its push into radiotherapeutics. In October, the drug giant struck a $2.1 billion deal to acquire Endocyte, the maker of a late-stage candidate for prostate cancer that combines the tissue-killing power of radiation with a small molecule that binds preferentially to tumor cells. And less than a year ago, Novartis paid $3.9 billion to get hold of Lutathera (lutetium Lu 177 dotatate), a first-in-class peptide-based radionuclide therapy and the first approved by the US regulators, by acquiring the French company Advanced Accelerator Applications (AAA), based in Saint-Genis-Pouilly.

Experts in nuclear medicine see both these investments as validation for a therapeutic strategy that struggled for decades to move beyond radioactive iodine-131, a staple of thyroid cancer treatment since the 1940s. "It's been a long struggle," says Jim Ballinger, a nuclear medicine researcher at King's College London. "It's good to see that some products have been successful and taken on by big pharma."

In fact, Novartis's decision to snag Endocyte now, without waiting for phase 3 trial results, was unusual. "Clearly they have confidence that they think it will work," notes David Nierengarten, a biotech analyst at Wedbush Securities in San Francisco.

Part of the reason industry has been slow to embrace radionuclide therapy may be the nascent nature of the technology itself: it needed a couple of decades to mature from the earliest efforts at labeling cancer-targeted agents with tumor-killing radioisotopes. "We have better tools now for developing these products," says Roy Larsen, a radiochemist and biotech entrepreneur, who, alongside Øyvind Bruland, a clinical oncologist at the University of Oslo, cofounded the Norwegian startup Oncoinvent, which is developing a radium-224–based cancer drug. Larsen and Bruland also cofounded two other radiotherapeutics companies, Algeta and Nordic Nanovector.



Stem Jems / Science Source

Prostate cancer cells, the target of Endocyte's radioligand therapy, which attaches a radioactive atom to a small molecule designed to bind PSMA, a protein highly expressed on this type of cancer cell but absent on most healthy tissue.

Lutathera's landmark approval by the US Food and Drug Administration came through in January 2018. But before it, US and European regulators had already granted marketing authorization to a few radiolabeled salts and antibody drugs. Most of these early radiopharmaceuticals proved to be commercial duds, however. The first, a samarium-153–tagged bone-seeking compound called Quadramet (samarium Sm 153 lexidronam), offered only palliative relief for cancer bone pain and never posted sales over $10 million per year. Then came two radiolabeled CD20-directed antibody drugs, Zevalin (ibritumomab tiuxetan) from IDEC Pharmaceuticals (now part of Biogen) and Bexxar (tositumomab and iodine I 131 tositumomab) from GlaxoSmithKline. Neither gained any market traction owing to competition with the blockbuster anti-CD20 agent Rituxan (rituximab). Biogen Idec soon sold off its asset, and GlaxoSmithKline eventually quit making Bexxar altogether.

The first commercial success came with Xofigo (radium Ra 223 dichloride), a calcium-mimicking salt that localizes to bone and

Table 1 Selected radiotherapeutics on the market or in late-stage development

Product	Lead manufacturer	Mechanism of action	Isotope	Disease(s)	Stage[a]
Quadramet	Lantheus Medical Imaging	Tetraphosphonate targets sites of new bone formation	Samarium-153	Cancer bone pain	Approved (1997)
Zevalin	Spectrum Pharmaceuticals	Ibritumomab targets CD20 on B cells	Yttrium-90	Non-Hodgkin's lymphoma	Approved (2002)
Bexxar	GlaxoSmithKline	Tositumomab targets CD20 on B cells	Iodine-131	Non-Hodgkin's lymphoma	Approved (2003; withdrawn 2014)
Xofigo	Bayer	Calcimimetic localizes to bone	Radium-223	Prostate cancer with bone metastases	Approved (2013)
Lutathera	Novartis	Octreotate targets somatostatin receptors	Lutetium-177	Gastro-entero-pancreatic neuroendocrine cancers	Approved (2018)
Azedra	Progenics Pharmaceuticals	Iobenguane targets norepinephrine transporters	Iodine-131	Adrenaline-producing neuroendocrine cancers	Approved (2018)
177Lu-PSMA-617	Endocyte	PSMA-617 targets prostate-specific membrane antigen on tumor cells	Lutetium-177	Castration-resistant prostate cancer	Phase 3
Iomab-B	Actinium Pharmaceuticals	BC8 targets CD45 on hematopoietic cells	Iodine-131	Bone marrow ablation before hematopoietic stem cell transplantation	Phase 3
Betalutin	Nordic Nanovector	Lilotomab targets CD37 on B-cells	Lutetium-177	Follicular lymphoma	Phase 2b (pivotal)

Source: Spotlight on radiotherapeutics: a Thomson Reuters Pharma Matters report
[a]Approval dates reflect marketing authorization from the FDA.

First edible cottonseed go-ahead

US regulators in October approved a transgenic cotton plant that produces edible seed. The plant, developed by Texas A&M AgriLife Research in College Station, is genetically engineered to greatly reduce the expression of the antinutrient gossypol in its seed, making it edible for humans and animals. Gossypol is a naturally occurring plant pigment produced in the glands of cotton that is toxic to insects and serves as a natural defense mechanism against pests. The pigment can also be toxic to humans and most monogastric animals, such as pigs, birds, fish and rodents, when consumed at high levels. Keerti Rathore and his colleagues at Texas A&M modified the cotton (*Gossypium hirsutum*) by silencing, with RNA interference, the genes in the seed that encode δ-cadinene synthase, a key enzyme in gossypol biosynthesis. This lowers gossypol in the seed by 97%, to 300 parts per million—below the US Food and Drug Administration's safety threshold. The rest of the cotton plant maintains normal levels of gossypol, enabling the plant to keep its inherent pest defenses. The technology could increase the value of cottonseed to farmers and others along the commercial chain, and provide a new protein source for humans and animals, Rathore says. The cotton plant triggered regulatory oversight by the US Department of Agriculture (USDA) because it was transformed using *Agrobacterium tumefaciens*, which the agency considers a "plant pest." The agency in August also approved for commercialization genetically engineered canola seed with increased levels of docosahexaenoic acid (DHA), an omega-3 fatty acid, developed by Nuseed in Breckenridge, Minnesota. Meanwhile, the USDA has increasingly given free passes to plants genetically altered using CRISPR, enabling the plants to be commercialized without the agency's oversight (*Nat. Biotechnol.* **36**, 6–7, 2018). That includes, most recently, a camelina line from Yield10 Bioscience in Woburn, Massachusetts, and a pennycress line from Illinois State University in Normal, Illinois, both with undisclosed phenotypes.

Emily Waltz

"I'm extremely worried that if we don't adapt the approach to reimbursement soon, we may foreclose the therapeutic opportunities." FDA Commissioner Scott Gottlieb, referring to CAR-T therapies. (*STAT*, 24 October 2018)

"We should expect AI merely to try its best to give us exactly what we ask for, and we should be very careful what we ask for." Janelle Shane comments on the darker side of machine learning. (*The New York Times*, 28 October 2018)

helps extend the survival of men with prostate tumors that have metastasized there. Bayer of Leverkusen, Germany, initially joined with the drug's originator, Algeta, to run phase 3 trials for Xofigo. But after the drug's approval in 2013, Bayer bought its partner outright for nearly $3 billion—and Bayer continues to be active in radionuclide drug development today.

Novartis's foray into radiopharmaceuticals is not recent: it began in the late 1990s, when it coupled its drug Sandostatin (octreotide), a somatostatin analog, to a radioactive warhead. Sandostatin had been used for decades to block hormone release in endocrine tumors. With the yttrium-90 ions, the drug—called 90Y-DOTATOC or OctreoTher—did more than block somatostatin receptors; it actively destroyed the types of neuroendocrine tumors that express these receptors on their cell surfaces.

After testing OctreoTher in more than 300 patients—around one-quarter of whom responded to the therapy—Novartis filed for marketing consideration with the FDA. The agency said no, though. According to David Bushnell, a nuclear medicine doctor at the University of Iowa Carver College of Medicine in Iowa City who led trials with the drug, the FDA wanted to see randomized clinical data before granting approval.

Novartis opted instead to offload the drug on Molecular Insight Pharmaceuticals, a company with a radionuclide therapy called Azedra (iobenguane I 131) in phase 1 testing at the time. Molecular Insight was acquired in 2013 by Progenics Pharmaceuticals; and in July 2018, Azedra—a conjugate of iodine-131 with an norepinephrine analog—won FDA approval for treating two types of rare adrenaline-producing neuroendocrine cancers. OctreoTher never advanced much further in these companies' hands.

Novartis only returned to radiotherapeutics a decade later, after AAA did the heavy lifting for them. AAA tested Lutathera in a randomized trial in patients with metastatic midgut neuroendocrine tumors. Compared with the control arm, Lutathera dramatically extended progression-free survival with no evidence of kidney damage thanks to the administration of protective amino acids (*N. Engl. J. Med.* **376**, 125–135, 2017).

"That's fairly unprecedented," says Jonathan Strosberg, a neuroendocrine tumor specialist at the Moffitt Cancer Center in Tampa, Florida, who led that phase 3 trial. Those data formed the basis of the FDA's approval, in January 2018, for Lutathera to treat neuroendocrine tumors of the gastrointestinal tract and pancreas.

Lutathera also couples a somatostatin analog to an isotope that emits high-energy beta particles. But instead of yttrium-90, Lutathera uses lutetium-177, a lower energy isotope that avoids some of the collateral damage to neighboring tissues. Lutetium-177 also has a longer half-life—about 6.6 days, compared with 2.7 days for yttrium-90—which means it "can be prepared centrally and distributed ready to use, avoiding uncertainties and logistics of on-site preparation," says Ballinger.

Plus, since lutetium-177 emits low levels of gamma rays on top of its higher energy beta rays, Lutathera can be tracked inside the body via single-photon emission computerized tomography. "You can watch the thing work," says Michael Tweedle, of the Ohio State University in Columbus, who, as president of Bracco Research USA, previously helped develop a lutetium-177–labeled drug for targeting gastrin-releasing peptide receptors on tumor cells. "It allows you get dosimetry data on a patient-by-patient basis," he says.

Lutetium-177 also underpins Endocyte's lead candidate, 177Lu-PSMA-617, which pairs the isotope with a small molecule designed to bind prostate-specific membrane antigen (PSMA), a protein highly expressed on the surface of prostate cancer cells. The drug was developed by ABX of Radeberg, Germany, and licensed in October 2017—but much of the PSMA-targeting technology actually comes from the laboratory of Philip Low, director of the Purdue University Institute for Drug Discovery in West Lafayette, Indiana, who founded Endocyte in the mid-1990s and has served as the company's CSO for the past 20 years.

An earlier PSMA-targeted small-molecule developed by Endocyte, EC1169, had, however, failed to shrink tumors in phase 1 testing. The agent, a microtubule inhibitor paired to a targeting ligand, zeroed in on prostate tumor cells as it was supposed to, but once there, didn't seem to release the therapeutic cargo.

Fortunately, the targeting part of the radiolabeled agent 177Lu-PSMA-617, which Low describes as "almost identical" to Endocyte's earlier compound, shouldn't suffer the same issue. "All you have to do is locate the lutetium near the cancer cell; you don't have to release it within the cancer cell," says Low. "That distinction simplifies the therapeutic mechanism enormously." Endocyte's 750-person, phase 3 VISION study for 177Lu-PSMA-617 began enrolling patients earlier this year. Other radiolabeled products in pivotal testing are Actinium Pharmaceuticals' Iomab-B, which directs lutetium-177 to CD45-expressing B cells in follicular lymphoma; and Nordic Nanovector's 177Lu-lilotomab satetraxetan (Betalutin), which uses iodine-131 to destroy the bone marrow ahead of stem cell transplantation (**Table 1**).

Other radioisotopes, such as rhenium-188, are also starting to come into favor. Rhenium-188 is a beta emitter, like lutetium-177. But because it radiates at least twice as far into surrounding tissues, "it has a better chance of penetrating the interior of a solid tumor," says Chris Adams, founder and CEO of Andarix Pharmaceuticals, which is using rhenium 188 P2045 (Tozaride) to target somatostatin receptor–bearing cells. The drug is currently in phase 2 for small-cell lung cancer.

Much of the action today, though, focuses on alpha particle emitters. "That's really the future," says Erik Mittra, a nuclear medicine specialist at the Oregon Health & Science University in Portland. These isotopes, such as bismuth-213 and actinium-225, can release ten or more times as much energy as beta emitters, and the particles travel a tiny fraction of the distance, no further than about a few cell diameters. That means that "with good targeting," says Bruland, chief medical officer of Oncoinvent, "you can irradiate very small volumes of cancer without damaging normal tissues." The challenge remains overcoming target heterogeneity within cancers and controlling the 'recoil' energy of alpha decay, which can still yield daughter radionuclides that may do serious harm to healthy tissue. "It has to be handled very carefully," Mittra says.

Even with beta emitters, there are ways to deliver bigger radioactive payloads to the tumors. One approach involves simply upping the dose. Reporting in October at the European Society for Medical Oncology 2018 Congress in Munich, Germany, Scott Tagawa, a urologic oncologist at Weill Cornell Medicine in New York, showed that men with metastatic prostate cancer could tolerate a fractionated dose of 177Lu-PSMA-617 more than three times higher than what participants are getting in the phase 3 VISION trial. "And we could have gone higher," Tagawa notes, since his study reached its maximum planned escalation with no dose-limiting toxicities.

So why is the trial using this lower dose? Because that's what doctors have always done, says Tagawa. Neither ABX nor Endocyte ever conducted a systematic dose-escalation study with 177Lu-PSMA-617.

Tagawa is also evaluating the potential of combining two different lutetium-177–labeled PSMA-targeted agents for treating prostate cancer: 177Lu-PSMA-617 and a similar antibody-based therapy from Telix Pharmaceuticals of Melbourne, Australia. The hope, Tagawa says, is that the different circulatory dynamics and PSMA-binding preferences of the small peptide and large antibody carriers will complement each other.

Meanwhile, Bushnell and his colleagues at the University of Iowa's Holden Comprehensive Cancer Center are running a dual radioligand therapy trial of their own for patients with midgut neuroendocrine tumors. That trial involves two different beta-emitting isotopes tethered to two different tumor-targeting peptides. On the basis of a tumor's profile of norepinephrine transporters and somatostatin receptors, as revealed through imaging, participants will receive customized doses of both an Azedra- and OctreoTher-like therapy. "You wind up being able to deliver higher radiation to tumors without exceeding any kind of safety limits," Bushnell explains. "It's a pretty slick little deal."

"You wind up being able to deliver higher radiation to tumors without exceeding any kind of safety limits."

For Novartis, the decision to buy Endocyte largely boiled down to the company's radiopharmaceutical assets—177Lu-PSMA-617 and a preclinical variant with actinium-225 labeling of the same PSMA-targeted small molecule. But Endocyte has also been working on ways to make chimeric antigen receptor (CAR) T-cell therapies safer and more controllable. As the maker of Kymriah (tisagenlecleucel), the world's first approved CAR-T product (*Nat. Biotechnol.* **35**, 691–693, 2017), Novartis could find that technology coming in handy.

Elie Dolgin *Somerville, Massachusetts*

RNAi biotechs flush with pharma dollars

Two deals riding on the coattails of Alnylam Pharmaceuticals' first US approval for an RNA interference drug have seen billions flowing into the space. In October, Janssen Pharmaceuticals paid Arrowhead Pharmaceuticals $175 million in cash for rights to an RNAi product designed to silence two regions in the hepatitis B virus (HBV) genome, in a deal worth up to $1.6 billion. The deal followed the release of striking interim results from a phase 1/2 trial with the biotech's ARO-HBV (AROHBV1001) candidate. In the same month, Dicerna Pharmaceuticals received $100 million up front and $100 million in equity investment from Eli Lilly to use Dicerna's GalXC RNAi platform for generating oligonucleotide therapeutic agents in cardiometabolic disease, neurodegeneration and pain. Arrowhead's study in eight HBV-infected patients achieved a 96–99% drop in circulating HBV surface antigen in the groups treated with the two lowest doses of the drug. Chronic HBV infection can lead to cirrhosis and liver cancer. Standard of care requires long-term treatment with PEGylated interferons or oral nucleoside or nucleotide analogs, which stop viral replication.

The recent results are remarkable considering that in November 2016 Arrowhead's intravenous delivery vehicle for a second-generation RNAi drug was found to be toxic to nonhuman primates. The FDA put a stop on Arrowhead's phase 2 trial of the drug, and the company's stock plummeted. Arrowhead decided to abandon the programs and develop a new delivery technology, Targeted RNAi Molecule (TRiM), which they used to develop the candidates tested in the most recent trial. ARO-HBV contains two siRNAs. Arrowhead was due to present more AROHBV1001 trial data at the Liver Meeting in November, as *Nature Biotechnology* went to press.

Dicerna also entered a deal with Alexion Pharmaceuticals in late October focused on the discovery and development of RNAi therapies to block the uncontrolled complement activation that drives many diseases. Dicerna received $22 million up front and an equity investment of $15 million, with potential for additional milestones and royalties.

Joana Osorio

"The goal of the college is to **"educate the bilinguals of the future."** MIT president L. Rafael Reif coins the term 'bilinguals' for people in fields like biology, chemistry, politics, history and linguistics who are also versed in modern computing techniques, in his announcement of a $1 billion college for artificial intelligence. (*The New York Times*, 15 October 2018)

"Science at this level is like a battleship, and it's really hard to turn it around. People get emotionally invested, financially invested, professionally invested." Jonathan Moreno, a professor of bioethics at the University of Pennsylvania, speaking of the fall from grace of cardiac stem cell researcher Piero Anversa. Some 31 research articles on cardiac stem cells from Anversa's lab could be retracted. (*The New York Times*, 29 October 2018)

"Some terms such as fake, synthetic and artificial meat are not just intended to cast our products in a negative light, they are also false and misleading. We are making real meat and seafood, and that's the whole point." Memphis Meats' Eric Schulze says biotechs are adamantly opposed to the term "lab-grown" while bemoaning the lack of new regulation for labeling cell-based meats. (*Food Navigator*, 25 October 2018)"