that, to maximize the therapeutic effect, you want high tumor penetrance with strong target affinity for a long dwell time, but rapid clearance from non-target tissues. The Aktis executives declined to specify the nature of their binding technology, but noted that the platform has never been used in oncology before.

Some of the disclosed targets in the crosshairs at other radiopharmaceutical companies include cell surface molecules overexpressed in tumor tissues: targets such as gastrin releasing peptide receptor (Novartis's ^{177}Lu-NeoB), the C-X-C chemokine receptor type 4 (Pentixapharm's PentixaTher), CD37 (Nordic Nanovector's Betalutin) and HER2 (Bayer's BAY 2701439). Other targets—including fibroblast activation protein (FAP), various integrins and carbonic anhydrase IX—are more tumor-associated, found in the surrounding vasculature or stroma yet still good candidates for targeted beta-emitting agents because of their proximity to cancer tissue.

As Germo Gericke, CMO of Advanced Accelerator Applications, a radiotherapy-focused subsidiary of Novartis (where Lutathera originated), points out: "You don't necessarily have to target the tumor. You can target an adjacent cell." In March, Novartis licensed a library of FAP-targeting agents that, like PSMA-617, originated at University Hospital Heidelberg and the German Cancer Research Center (DKFZ). Other companies, including Telix and Actinium Pharmaceuticals, are also pursuing targets found on hematopoietic cells, the idea being to prepare patients for bone marrow stem-cell transplants more safely and effectively than with current chemoablative conditioning regimens.

Most firms are beginning to explore rational drug combinations as well—pairing radiotherapeutics with, for example, checkpoint inhibitors, chemotherapy drugs or other radioactive agents. Some trials are also testing whether inhibitors of poly(ADP ribose) polymerase, a type of DNA damage response enzyme, can help prevent cells from fixing the destruction wrought by drugs like Lutathera and ^{177}Lu-PSMA-617. Novartis, through a research pact announced in April with Artios Pharma, is now planning to discover and develop more DNA repair inhibitors for combination regimens of its own.

But with added therapeutic complexity comes added potential for toxicity, warns Thomas Hope, a nuclear medicine specialist at the University of California, San Francisco. "A lot of the things that amplify the effects of radiation also cause marrow injury," he says, "so the hard thing is threading that needle of toxicity. It's a very careful game you have to play."

Another way to maximize therapeutic benefit, Hope notes, would be to administer targeted radiopharmaceuticals in non-conventional ways, either by playing with the dosage and schedules or by personalizing treatment plans on the basis of an individual's imaging results. At the moment, he says, "we are not leveraging the patient precision that we could have."

That's because the approved dosage regimen for Lutathera and the dosing protocol used in phase 3 studies of ^{177}Lu-PSMA-617 were each chosen for historical reasons. There were never any prospective dose-escalation studies before those strategies were chosen for late-stage testing. The companies simply took the approach favored by most doctors "and went with it," says Scott Tagawa, a urologic oncologist at Weill Cornell Medicine in New York.

Tagawa and his colleagues have since evaluated a new fractionation schedule, administering up to three times the standard dose of ^{177}Lu-PSMA-617 in two parts over two weeks, rather than giving the usual amount every six weeks for up to six cycles. There were no dose-limiting toxicities, he says, and patient outcomes, as measured by changes in prostate-specific antigen levels and median progression-free survival, were similar to those reported with the standard dosage regimen. His approach does offer the benefits of shorter treatment durations and lower healthcare costs (because of fewer hospital visits and less drug used overall), but would still need to be tested head to head to ensure the safety and efficacy are comparable.

"That fine tuning can certainly occur down the line," says Michael Morris, an oncologist at Memorial Sloan Kettering Cancer Center in New York City who led the scientific review committee for the phase 3 trial of ^{177}Lu-PSMA-617. He also presented the study results at the ASCO meeting. "In the meantime, this drug prolongs survival as given"—and that's welcome news, for patients and the growing number of radiopharmaceutical companies alike. ❐

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COVID vaccines grow on leaves

Canadian regulators have started a rolling review of a plant-made COVID-19 vaccine that has produced strong immune responses in a mid-stage clinical trial. Medicago, based in Quebec City, Canada, announced that after two doses, its vaccine candidate, mixed with GlaxoSmithKline's pandemic oil-based adjuvant AS03, met its goals in a phase 2 study. In the randomized, placebo controlled trial, after two doses of the vaccine, known as CoVLP, generated neutralizing antibody responses that were about ten times higher than in patients recovering from the virus. In addition, the vaccine stimulates a cellular immune response of the T helper-2 type (producing interferon-γ and interleukin-4), unlike other COVID-19 vaccines, which stimulate a T helper-1 response. The vaccine was well tolerated, with adverse effects mild to moderate. Medicago is arriving late to the pandemic vaccine response, but plant-based production holds the advantage that it can be rapidly scaled up and the vaccine, stored between 2 and 8 degrees Celsius, may be useful in varied environments. Results from phase 1 trials were published 18 May.

Medicago's platform uses living *Nicotiana benthamiana*, a relative of tobacco, as a bioreactor to manufacture non-infectious coronavirus-like-particles (CoVLPs). The plants are not genetically modified but transfected with full-length SARS-CoV-2 spike glycoprotein. The recombinant virus-like-particles self-assemble and bud off the plant cell surface, accumulating in the space between the plasma membrane and the cell wall. The leaves are blended to extract and purify the VLPs for use in the vaccine. The recombinant VLPs are non-infectious because they lack the virus's core genetic material, but still stimulate an immune response similar to that seen in a natural infection.

A phase 3 trial of the vaccine launched in March 2021, and a trial to test the vaccine against emerging variants has also begun. Medicago is jointly owned by Mitsubishi Tanabe Pharma and Philip Morris International.

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