New cancer drugs can wake up sleeping killer T cells
Frontline immune system fighters, often evaded by tumors, might now resume the attack

BY NATHAN SEPPA
Cancer relies on a bag of tricks that can render it virtually invisible to the body’s disease-fighting apparatus. Tumors even co-opt “checkpoint” proteins found on the immune system’s T cells. These proteins normally prevent the immune system from running amok. When activated, these checkpoints can turn a T cell from a bristling warrior ready for a fight into a dozing sentinel — and cancer takes full advantage.

Now, though, new drugs that disable these checkpoint proteins are showing a keen ability to awaken T cells and, in so doing, pull away cancer’s veil. In the last year, studies testing a handful of these drugs have demonstrated eye-opening results against melanoma — the deadly kind of skin cancer — and tangible gains against other malignancies.

The results have sent a jolt through a research community that had grown doubtful about harnessing the immune system to fight cancer. “The sun is finally rising,” says oncologist Michael Postow of Memorial Sloan Kettering Cancer Center in New York City. “I think this is going to be a big deal for a long time.”

Clinical trials reported in late 2014 suggested a high upside for checkpoint drugs in patients who had run out of options against melanoma and cancers of the kidney, bladder and lung (SN: 12/27/14, p. 8). And new studies presented at two recent cancer meetings have fed the optimism with promising results against those cancers and others. Some of the first trials combining two checkpoint stoppers in patients have yielded impressive results. And although the dual-dose approach causes some side effects, it is unclear whether these are worse than the downsides of chemotherapy.

In one study, Postow and an international team identified 945 people with inoperable melanoma that had spread to areas beyond the skin. The patients were given either ipilimumab or nivolumab or both. These drugs each target a distinct checkpoint protein on frontline troops, aptly named killer T cells. Nearly 58 percent of those getting both drugs showed substantial tumor shrinkage in subsequent months, the standard yardstick of a good response. Almost 44 percent of those getting just nivolumab saw their tumors shrink, as did 19 percent of patients receiving only ipilimumab, Postow and colleagues reported in May at a meeting of the American Society for Clinical Oncology in Chicago and in the New England Journal of Medicine.

Three other studies, all published in the New England Journal, have had revealing results as well:

- In a subset of patients with particularly difficult-to-treat melanoma, 44 of 72 getting the two checkpoint drugs had a good response compared with just four out of 37 getting ipilimumab alone, researchers reported in April at a meeting of the American Association of Cancer Research in Philadelphia.

- In patients with relapsed or unresponsive Hodgkin’s lymphoma, 11 out of 23 showed improvement after 24 weeks on nivolumab and were able to stay on the drug; a few others who initially responded relapsed and two patients went off the drug because of side effects.

- In 272 lung cancer patients with a poor prognosis, nivolumab by itself outperformed the standard chemotherapy drug docetaxel; after one year, 42 percent of patients on the checkpoint drug were still alive compared with 24 percent of patients on the chemo drug. These results, presented at the Chicago meeting, are “pretty unheard of,” says study co-author Julie Brahmer, an oncologist at Johns Hopkins University.

For decades, immunotherapy to fight cancer has been marked by fits and starts (SN: 6/14/14, p. 22). Part of the problem seems to lie in the checkpoints themselves. It does little good to supercharge an immune response if killer T cells can be lulled to sleep on the job.

Lock and load In this computational image, a ligand protein binds to precise spots (yellow) on a T cell’s receptor protein PD-1, acting like a key in a lock. This activates PD-1 to send a signal that puts the T cell to sleep, making it oblivious to cancer. The precise modeling shown here may help researchers create drugs that disrupt the connection — awakening T cells and making cancer “visible.”
Checkpoint drugs inhibit the inhibitors of the immune system. The newer approach “releases the parking brake” on T cells that have reached a tumor only to turn quiescent, says Drew Pardoll, an immunologist and oncologist at Johns Hopkins.

Not all patients benefit from the checkpoint drugs, Pardoll says, in part because tumors have found several ways to sabotage immune reactions. But the early data suggest that 20 to 35 percent of cancer patients might benefit from overriding the checkpoints, he estimates.

The two best-understood checkpoint proteins are called PD-1 and CTLA-4. These T cell proteins are known as receptors. Other proteins called ligands fit precisely into receptors to activate them, instructing the T cell to nod off. It’s no accident that this happens at a tumor’s doorstep: Cancer can produce such ligands and induces immune cells to do the same.

By stopping this ligand–receptor interaction, the new drugs sabotage the checkpoint and awaken the killer T cells, which then identify cancerous cells and attack them. The veil is lifted.

Several pharmaceutical companies are working on prospective checkpoint drugs. It’s becoming clear that ipilimumab, which thwarts CTLA-4, is not as potent as either of the drugs that target PD-1—nivolumab and pembrolizumab. That may be because CTLA-4 often shows up on other T cells, not just the killer T cells on the front lines, and thus may have an indirect effect on the tumor. Other compounds being tested take aim at the ligands themselves.

Not surprisingly, scientists are testing these drugs on all kinds of malignancies. In urinary tract cancer patients, seven of 28 patients getting pembrolizumab showed a measurable improvement. In an ongoing study, the ligand-targeting drug candidate avelumab induced tumor shrinkage of 30 percent or more in at least 11 of 75 women with advanced ovarian cancer. And a small study of colorectal cancer patients finds that those with tumors harboring DNA-repair deficiencies fared better after getting a PD-1–blocking drug than did patients with normal DNA repair. This abnormality might enable doctors to identify colorectal cancer patients likely to benefit from PD-1 inhibition, Pardoll says.

Immune checkpoints serve a purpose, of course, acting as shutoff switches. This fail-safe characteristic — known as immune tolerance — is lacking in autoimmune diseases such as rheumatoid arthritis in which unbridled immune responses damage one’s own tissues. PD-1 and CTLA-4 are agents of immune tolerance, says Khaled Barakat, a physician who works on drug design at the University of Alberta in Edmonton, Canada.

The risk of collateral damage makes reducing immune tolerance in people a tricky business. The combination of ipilimumab and nivolumab hit cancer hard in the large melanoma trial, but it also resulted in side effects so severe that 36 percent of patients on the two drugs had to stop taking them before getting all the prescribed doses.

“Toxicity is greater with the combination,” Pardoll says. “Combo enthusiasts would say that if you know what you’re doing — and can manage to mitigate the side effects — you can get patients through in a vast majority of cases.”

Part of the problem could be the drugs themselves, which are monoclonal antibodies specifically aimed at these receptors or ligands. The drugs often act within weeks. But other times, responses seem delayed, Postow says, with tumor shrinkage that doesn’t show up until after patients have stopped taking the drugs. The reason is unclear.

Late benefit is better than none, but it creates uncertainty in how best to prescribe the drugs and still manage the side effects. Brahmer says the antibodies themselves don’t linger in the system. “We think we’re creating memory in the T cells, so they remember what they are supposed to be targeting,” she says. “But the side effects can linger.”

Barakat says a better approach might be to use faster-acting drugs that risk fewer side effects. His lab is embarking on a five-year quest to come up with compounds that hit receptors and ligands with more precision and quell the checkpoints for shorter periods. This “small-molecule” approach might also unearth compounds that can reach walled-off parts of the body, such as the brain.

Cancers don’t respond uniformly to the checkpoint antibody drugs. But some tumors that show early exciting responses are heavily mutated, Brahmer says, such as melanoma (with DNA mutated by ultraviolet rays) and lung cancer (DNA mutated by cigarette smoke). Such tumors might give off a lot of antigens, molecules that draw immune attention. These antigens cause immune forces to mass, possibly providing an army that’s ready to go when a checkpoint gets lifted.

Meanwhile, researchers are combining the new drugs with radiation and other cancer treatments. Radiation might harass a tumor into producing more antigens, which could boost the impact of checkpoint drugs, Brahmer says.

With each positive finding, immunotherapy gains some credence. There was a time when other scientists “thought immunotherapists were a little bit crazy,” Brahmer says. “People who weren’t believers are becoming believers now.”