



Mutations that hit coding genes can result in the production of aberrant proteins.



LUIS DIAZ

TUMOR TARGETER

About four years ago, Luis Diaz walked into Bert Vogelstein's office at Ludwig Johns Hopkins and announced that he'd just had something of a scientific insight. Diaz, an oncologist and accomplished cancer geneticist, had been watching the progress of a class of cancer immunotherapies known as checkpoint blockade with a touch of surprise. As the son of a prominent immunologist, he had grown up virtually breathing immunology and had an instinctual feel for the subject. "I often say that immunology is my hobby," he says. "But I'd always believed it would be very tough to elicit an immune response against a tumor. In fact, until relatively recently, I didn't think we'd ever have an immunotherapeutic approach that would work."

Now, Diaz told Vogelstein, co-director of Ludwig Johns Hopkins, he thought he knew why antibodies against a protein named programmed death-1 (PD-1) were eliciting intense anti-tumor immune responses in some patients. The cancer cells in responsive patients, Diaz suspected, were laden with many more mutations across their genomes than those of patients who had not responded to the therapy. This suggested, he said, that cancers of any type that are deficient in their ability to repair DNA might be susceptible to checkpoint blockade.

His hunch laid the foundation for a clinical trial whose results—reported at the 2015 American Society for Clinical Oncology Annual Meeting

and published in the *New England Journal of Medicine (NEJM)*—thrilled the oncology community. Diaz and his colleagues found that, regardless of their tissues of origin, tumors whose cells are deficient in repairing mismatched DNA sequences, and so preventing a gross accumulation of mutations, are far more susceptible to the anti-PD-1 antibody pembrolizumab than those that retain this ability. Equally important, candidates for such treatment can be easily identified by genetic tests that have been on the market for about two decades.

From hallway to clinic

Diaz's hypothesis may have been a mite premature back in 2012, but he and

Vogelstein nonetheless shot off a letter on the matter to NEJM. The journal promptly rejected their proposal.

Still, Diaz believed he was onto something, and he had found an enthusiastic sounding board for his ideas. Vogelstein—and, independently, Ludwig San Diego Director Richard Kolodner—had in the early 1990s discovered the genetic basis of an inherited propensity for colon cancer known as Lynch syndrome. They had shown that Lynch patients had defects in genes that repair DNA, making them prone to

mutations of all sorts, including those that cause cancer.

Diaz, who specializes in treating colon cancer, also knew that the tumors of Lynch patients tended to be highly infiltrated with immune cells and that these patients live longer with their cancers than do most other colon cancer patients. Meanwhile, clinical studies were showing that melanomas respond quite well to PD-1 blockade. These tumors, like those of tobacco-related lung cancers, are known to have highly mutated cells.

He and Vogelstein began discussing the idea with colleagues at Johns Hopkins. They learned in those discussions that anti-PD1 antibodies had generally failed to induce responses in one trial involving colon cancer patients. But, in a casual hallway conversation, Diaz learned that one patient out of the 33 enrolled in that trial had in fact responded rather well. Diaz asked that the tumor sample from that patient be tested for its mutational load.

“Colon cancer cells typically only have a few dozen mutations,” says Diaz. “But we

were thinking, maybe that patient’s tumors had mismatch repair deficiencies and would harbor thousands of mutations per cell. And, lo and behold, that turned out to be the case.”

Excited, Diaz and Vogelstein asked Merck—which makes pembrolizumab—and other companies making anti-PD-1 antibodies whether they would be interested in supporting a trial testing his idea. The answer was, uniformly, no. Coaxed and cajoled by Diaz, however, Merck finally gave in a little: it would donate the drug, but Diaz would

have to find the funding elsewhere and agree to sponsor the trial—accepting liability and responsibility for its management.

“Fortunately,” says Diaz, “we got support for the trial from the philanthropy Swim Across America, which, along with Ludwig, supports my research. We were able to run the trial on a shoestring budget.”

Green lights

Diaz recruited a young gastrointestinal oncologist, Dung Le, an assistant professor of oncology at Johns Hopkins, to lead the study with him. Their clinical trial involved three cohorts from a total of 41 patients, all of whom had very advanced cancers. One included patients with colon cancer that was deficient in DNA repair. The second enrolled patients with a variety of other cancers that were similarly dysfunctional, while the third included colon cancer patients whose tumors were proficient in such repair. All patients were given pembrolizumab, after which they were evaluated for reduction in

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tumor size (immune-related objective response rate, or irORR) and for progression of disease at 20 weeks (progression-free survival, or irPFS).

The results were stunning. The DNA repair-deficient colon cancer patients, many of whom were at death’s door when they entered the trial, had an irORR of 40% and an irPFS of 78%. Patients with other DNA repair-deficient cancers had an irORR of 71% and an irPFS of 67%. None of the colon cancer patients whose tumor cells could repair DNA responded to the therapy, and this cohort’s irPFS at 20 weeks was only 18%. Diaz and his colleagues reported that DNA repair-deficient tumors harbor more than 20 times as many mutations as proficient ones. High rates of mutation, they found, are associated with prolonged progression-free survival following PD-1 blockade.



Luis Diaz
Ludwig Johns Hopkins

That makes sense. Mutations that hit coding genes can result in the production of aberrant proteins. These may be seen by the immune system as foreign, prompting a response lethal to cancer cells. It is this response that would be further stimulated by checkpoint blockade.

Merck was excited by the results: It immediately launched two large scale trials led by Diaz and Le to obtain regulatory approval for the therapy, one of them as first-line therapy for DNA repair-deficient colon cancers. The US Food and Drug Administration was impressed as well. It gave the therapy “breakthrough” status in November to speed its path to the clinic.

“Right now our focus is on colon cancer,” says Diaz, “but I can tell you that this

is probably going to be tumor-type independent, as this genetic marker is found across a variety of cancers. We think the eligible patients may represent as many as one in 25 of all cancers.”

Diaz, for his part, is most excited for his patients.

“I would walk into the room of a man who was being consented for hospice, give him a drug and watch his tumor melt away,” says Diaz, recalling the thrill of the trial. “These patients typically had just weeks to live when they enrolled. More than half of them had a major response to the therapy. Some had complete responses. It’s still very satisfying to continually interact with people who would not be living today if they hadn’t been offered this therapy.” ■