Go van Dam would have homed in on the cancer cells. If engineered CAR T cells designed to bind FITC had been injected into the patient, they would have homed in on the cancer cells.

In a patient with ovarian cancer, malignant nodules have taken up the folate-FITC adapter. In another patient, two different tumors were found; they're thought to preferentially arise, and whether secondary resistance mechanisms leading to new lesions—both of which could benefit from using CAR T cells—occurs in about 25% of patients who initially respond well to immune escape mechanisms may exist. The researchers did not find any mutations in the fourth patient, he adds.

How Melanoma Resists PD-1 Blockade

A study from researchers at the University of California, Los Angeles (UCLA), sheds light on mechanisms by which melanoma cells become resistant to PD-1 blockade (N Engl J Med 2016 July 13 [Epub ahead of print]). Delayed relapse, or secondary resistance, occurs in about 25% of patients who initially respond well to immune checkpoint inhibition,” says senior author Antoni Ribas, MD, PhD, director of UCLA’s tumor immunology program. “Why this happens is largely unknown.”

Ribas’s group studied four patients with metastatic melanoma who achieved objective responses to pembrolizumab (Keytruda; Merck), but who experienced tumor recurrence after a median time of nearly 1.8 years, despite continuous therapy. The researchers carried out whole-exome sequencing of tumor tissue obtained from these patients before treatment and after disease progression. The recurrent tumors of two patients had loss-of-function mutations in JAK1 and JAK2, respectively; a third had a truncating mutation in B2M.

“These were newly acquired, homozygous mutations,” says Jesse Zaretsky, the study’s first author. “To mutate one allele, lose the other wild-type copy, and duplicate the mutated allele involved considerable work on the tumor’s part, suggesting strong selective pressure after checkpoint inhibition.” None of these alterations were found in the fourth patient’s recurrent tumor, he adds.

In the first two patients, melanoma cells became “selectively deaf” to antiproliferative signaling through interferon-γ, which requires intact JAK1 and JAK2, Zaretsky says. On balance, such growth-curbing effects are usually acceptable to a tumor because interferon-γ signaling also upregulates PD-L1, enabling evasion of immune scrutiny, Ribas says. However, with pembrolizumab added to the picture, “continued PD-L1 production would be futile,” he explains, “and the other associated effects of interferon-γ signaling would become a liability. We think these tumors figured out that abolishing this pathway’s activity altogether, by inactivating JAK1 or JAK2, was more advantageous.”

B2M’s protein product, beta-2-microglobulin, is necessary for the proper folding and transport of MHC class I molecules, which present foreign antigens to the immune system, to the cell surface. Consequently, cytotoxic T cells with mutant B2M no longer recognize and targeted the melanoma cells for destruction, Zaretsky says, even with continued PD-1 blockade exposing the tumor to immune surveillance.

Although the researchers did not find any mutations in the fourth patient that were clearly linked to secondary resistance, Ribas points out that other nongenetic immune escape mechanisms may exist. Meanwhile, a larger sample size is needed to determine the frequency of JAK1/2 and B2M mutations in pembrolizumab-resistant patients, he adds.

Thomas Gajewski, MD, PhD, an immunologist at the University of Chicago in Illinois, thinks this study raises “several interesting next-level questions,” including precisely how the genetic variants identified by Ribas’s group arise, and whether secondary resistance mechanisms leading to new lesions—not just recurrence at existing metastatic sites—are similar or different. “Oncolytic viruses could be a therapeutic option in the JAK1/2-mutant setting; they’re thought to preferentially replicate in tumor cells with blunted
ever happening.” Gajewski observes. “Overall, though, it’s important to consider combination immunotherapy early in the disease course. Eliminating the majority of tumor cells quickly, before extensive genetic variants emerge, may prevent secondary resistance from ever happening.” —Alissa Pob

NIH Prepares to Launch Precision Medicine Study

The NIH recently awarded $55 million to several institutions to launch its Precision Medicine Initiative Cohort Program (PMI-CP), which aims to enroll at least 1 million Americans by 2020 in a long-term study starting this fall. The PMI-CP will collect genetic information on participants along with their answers to a variety of questions about their lifestyle, behavior, and environment. They will also be asked about their health history, to contribute blood and urine samples for analysis, and to grant access to clinical data stored in their electronic health records.

The project has far-reaching implications for studying cancer and other diseases, says Joni Rutter, PhD, director of the Division of Programs and Strategic Implementation for the PMI-CP. “The comprehensiveness of the program and variety of information to be collected are unmatched,” she says. “It will allow scientists to identify new ways that these factors may be associated with one another and how they might impact diseases like cancer.”

With the PMI-CP, “we aim to achieve quadruple diversity—of people, health conditions, geographic areas, and data types—to build a rich resource for future studies,” adds Eric Dishman, PhD, PMI-CP director.

A unique feature of the project is allowing researchers and the public to access and view deidentified data via a secure website, as opposed to downloading files, says Rutter. Once approved for access, users will be able to identify and analyze the data pertaining to their research questions.

The project will facilitate cooperation among cancer researchers, says Roy Herbst, MD, PhD, chief of medical oncology at Yale Comprehensive Cancer Center in New Haven, CT. “We’re not finding many new genes through individual sequencing studies,” he says.

“These new centers will make it easier to collaborate and combine data with other research centers, which is especially important for rare cancers.” In May, the NIH awarded Rochester, MN–based Mayo Clinic $142 million over 5 years to create a biobank to collect, store, analyze, and distribute biospecimens. The latest funds will support development of three additional centers and/or partnerships:

- **The Data and Research Support Center** will organize and store data sets. It will also provide research support and analytic tools to researchers and the public. (Awarded to Vanderbilt University Medical Center in Nashville, TN, in collaboration with the Broad Institute in Cambridge, MA, and Verily Life Sciences in Mountain View, CA.)

- **The Participant Technologies Center** will support direct enrollment of participants and develop mobile applications to collect data from and communicate with them. (Awarded to Scripps Research Institute in San Diego, CA, and Vibrent Health in Fairfax, VA.)

- An initial set of healthcare provider organizations will assist with enrollment. It includes four regional medical centers and their collaborators (Columbia University Medical Center in New York, NY; Northwestern University in Chicago, IL; the University of Arizona in Tucson; and the University of Pittsburgh, PA), six community health centers, and Veterans Administration medical centers. —Janet Colwell

Greenebaum, Stanford Earn Comprehensive Status

The NCI has granted Comprehensive Cancer Center status to the University of Maryland’s Greenebaum Cancer Center in Baltimore and to the Stanford Cancer Institute (SCI) in Palo Alto, CA. They join 45 other centers that have earned the agency’s highest distinction—recognition of their leadership in research, education, and clinical care.

Currently, 69 institutions with strong basic and clinical research programs have been named NCI-Designated Cancer Centers. Comprehensive status requires additional breadth and depth: Institutions should not only bridge their basic and clinical research, but also demonstrate the ability to connect these programs to their local populations. Greenebaum became an NCI-designated center in 2008 and subsequently expanded its activities—particularly in population science and clinical trial recruitment—to qualify for the higher ranking, says Director Kevin Cullen, MD.

“We have focused heavily on improving health disparities in cancer research and access to treatment, especially among African-Americans,” Cullen says. “Our population-science program is a big part of that and was a key component in moving us toward this designation.”

Nearly 33% of participants in Greenebaum’s clinical trials are African-American, compared with about 2% nationally—a testament to strong community ties, Cullen says. The Baltimore City Cancer Program offers breast, cervical, and colon cancer screening to uninsured and underinsured area residents. Those diagnosed with cancer receive information about clinical trials and enrollment assistance.

In addition, Greenebaum has built a network of partnerships with health centers and physicians across the state aimed at increasing access to trials in nonurban areas, which also helps facilitate population-based research, says Edward Sausville, MD, PhD, associate director for clinical research.

“Eighty percent of our referrals come from the city of Baltimore and 10 adjacent Maryland counties,” Sausville says. “Comprehensive designation will certainly be a basis for continuing to build alliances in those areas in order to ensure that all citizens of Maryland have the opportunity to consider clinical trial participation.”

Always strong in basic science, SCI was named an NCI-Designated Cancer Center in 2007. Garnering comprehensive status “was a matter of building our clinical research enterprise, recruiting physicians who are also superb researchers, and building our population-science program,” says Director Beverly Mitchell, MD.

The Stanford Cancer Initiative, launched in 2013, boosted the institute’s recent NCI review. The initiative “applies rigorous research analysis to every aspect of patient care in order to identify which modalities improve the care experience,” Mitchell explains. For
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