Patient’s T Cells Target Tumor Mutation

Researchers at the NCI have raised an army of immune cells that specifically target a mutation unique to a patient’s tumor, leading to the regression of a metastatic epithelial cancer.

Until now, adoptive cell therapy using tumor-specific immune cells—so-called tumor-infiltrating lymphocytes (TIL)—has been successful in treating only metastatic melanoma. The new research also marks the first time scientists have used T cells to intentionally home in on a tumor mutation.

The findings, published in May, outline the treatment of a 43-year-old woman with metastatic cholangiocarcinoma (Science 2014;344:641–5). Scientists extracted TILs from tumor samples taken from her lungs and cultured them in the lab. Whole-exome sequencing identified 26 nonsynonymous mutations harbored by her cancer. Further tests showed that a mutant ERBB2-interacting protein (ERBB2IP) was recognized by some of her TILs.

After receiving lymphocyte-depleting chemotherapy, the patient was infused with 42.4 billion TILs, about 10 billion of which were reactive to the mutated ERBB2IP. She then received four doses of IL2 to enhance T-cell proliferation and function.

The metastatic lesions shrank and then stabilized for about 13 months before progressing. The patient received a second treatment, this time with 126 billion TILs, about 95% of which were reactive to the mutated protein. Her tumors began shrinking within a month and continue to regress after 6 months, researchers report.

Steven Rosenberg, MD, PhD, the study’s senior author and chief of the surgery branch at the NCI’s Center for Cancer Research, calls it “the ultimate personalized treatment. This is a technique to develop a patient’s own T cells against mutated proteins within their own cancer.” His team is now working to streamline the complex process.

Rosenberg says immunotherapy has been most successful in melanoma, in part because melanoma has up to 10 times as many mutations as common epithelial malignancies such as breast, colon, and lung cancers. The new research could serve as a “blueprint” for these common tumors, he says. Epithelial cancers comprise more than 80% of all cancers and are responsible for about 90% of cancer deaths each year in the United States.

However, Rosenberg and other cancer immunotherapy experts caution that the research is early and involved only one patient.

Cassian Yee, MD, a professor of melanoma medical oncology and immunology who directs the Solid Tumor Cell Therapy program at The University of Texas MD Anderson Cancer Center in Houston, says it is unknown how many patients with epithelial cancers will have targetable mutations.

“Almost every tumor has mutations but not all are recognized by the immune system,” says Yee, who was not involved in the research. “Whether you can attack the tumor in the next patient who has different mutations and a different T-cell repertoire remains to be seen.”

Rosenberg and his colleagues should soon find out. They have pinpointed unique tumor mutations recognized by the immune system in two patients with colon cancer. “We’re now working to see if we can treat them,” he says.

Rules Proposed for Unregulated Tobacco

The FDA has proposed wide-reaching new rules that, if finalized, would ban the sale of e-cigarettes, pipe tobacco, cigars, and other tobacco products to minors. The regulations would also prohibit e-cigarette manufacturers from making claims about health benefits without first presenting supporting scientific evidence.

The measure marks the first time the agency has attempted to regulate e-cigarettes, a multibillion-dollar industry. The products’ popularity has grown rapidly in recent years, even among minors. According to data from the Centers for Disease Control and Prevention, the number of middle and high school students who have tried e-cigarettes doubled between 2011 and 2012.

“We’re certainly pleased that the FDA is doing this. We’ve been waiting on this for a long time,” says Lauren Dutra, PhD, an epidemiologist at the Center for Tobacco Control Research and Education at the University of California, San Francisco.

Dutra notes that the new laws would require manufacturers to print warnings about health consequences on the packaging for cigars and loose tobacco used for rolling cigarettes, a regulation applauded by tobacco-control advocates. E-cigarettes will not have to carry such warnings, as little solid evidence exists that they are harmful. However, they may be required to carry warnings about the addictiveness of nicotine.

Even so, Dutra and other tobacco researchers say the proposed measures don’t go far enough—and should have been passed years earlier.

“The action that the FDA took is long overdue,” says Dennis Henigan, JD, director of legal and policy analysis at the Campaign for Tobacco-Free Kids in Washington, DC. He notes that the FDA has had the authority to regulate tobacco products since 2009, when Congress passed the Family Smoking Prevention and Tobacco Control Act.

The 2009 act prohibited the use of flavors other than menthol in conventional cigarettes, but the proposed regulations will not extend that ban to e-cigarettes. E-cigarettes are often made with candy or fruit flavors, including mint, chocolate, cherry, and grape. Those flavors make tobacco products especially appealing to minors, say critics, just as they did with cigarettes in the past.

“There’s substantial documentation that the industry intentionally flavored cigarettes to attract kids,” says Henigan.

Mitchell Zeller, JD, director of the FDA’s Center for Tobacco Products, says that by regulating e-cigarettes and other products, “the FDA, as the science-based, independent gatekeeper, is by law standing between the companies and the users.”
The goal of regulation, Zeller says, is “to reduce the overall disease toll from tobacco use,” and he calls the proposed rules a “critical and essential foundational step.”

The FDA has the authority to ban flavoring or other ingredients for health reasons, Zeller says, if “we have the science to back it up.” Banning flavor would require a separate legal process which, he notes, can only begin once the FDA has jurisdiction over e-cigarettes, as outlined in the proposed rules.

The regulations are outlined in a “deeming” document released in April, available at www.federalregister.gov.

NIH Clinical Center Open to Collaboration

Under a new federal program, 10 research projects, including a few directly related to cancer, will receive $500,000 a year for at least 3 years and will give academic researchers access to the resources of the NIH Clinical Center in Bethesda, MD.

Researchers both inside and outside of government think the collaborations are a good idea.

“At a time when healthcare dollars are scarce, at a time when budgets are tight across the board, any opportunities to offer additional funding mechanisms to physician scientists are welcome,” says Peter Pinto, MD, a senior surgeon and principal investigator in the Urologic Oncology Branch of the NCI.

Pinto and his NCI research colleagues will collaborate with a team led by Arul Chinnaiyan, MD, PhD, a urologist and professor of pathology and urology at the University of Michigan at Ann Arbor, to combine advanced MRI and metabolic imaging with genomic sequencing to improve prostate cancer diagnoses and treatment.

In the first round of research, they plan to scan 60 patients scheduled for prostate surgery at the NIH Clinical Center and then ship tissue samples to the University of Michigan for genetic analysis, including whole-exome sequencing and RNA transcriptome analysis, looking for both DNA and RNA mutations.

“It’ll be a first-of-its-kind study, linking advanced molecular and metabolic imaging with comprehensive molecular, next-generation sequencing,” says Chinnaiyan.

The goal is to understand how genetics might be driving what scientists see in their images, he explains, and ultimately to find a signature for the 20% to 30% of prostate cancers that will turn dangerous if not treated.

Chinnaiyan says he and Pinto had talked about collaborating in the past, but the grant program “was a catalyst to get us to do something, versus talking about it. We never really got to doing this seriously until we received this grant.”

In another project, Yang Liu, PhD, a cancer biologist and immunologist at Children’s National Health System in Washington, DC, will be using a government-developed inhibitor to try to eliminate cancer stem cells from pediatric patients with acute myeloid leukemia (AML). Current treatment helps nearly 90% of pediatric AML patients, but nearly half relapse within 2 years, and more than half of those patients die within a few years.

Liu wants to test an investigational drug called echinomycin, which inhibits hypoxia-inducible factor, believed to be a driver of AML stem cells. The NIH tested echinomycin in the 1990s, but couldn’t measure its accumulation in tissue or blood and so couldn’t tell if it targeted the tumor. Liu says he’d received small amounts of the drug previously, but he had no money to formulate it. Now, with the new grant and collaboration, he can test its pharmacokinetics in nonhuman primates and develop it into a form he can give to children with AML.

“Without the NIH, we wouldn’t have the funds to formulate the drug in the form that we need,” Liu says.

Ramucirumab Approved for Gastric Cancer

On April 21, the FDA gave physicians the go-ahead to use ramucirumab (Cyramza; Lilly Oncology) as second-line therapy for patients with advanced stomach cancer or gastroesophageal junction (GEJ) adenocarcinoma. Ramucirumab is the first drug approved in this setting.

“The frequency of gastroesophageal junction adenocarcinoma is rising faster than any other cancer in the U.S., making this a public health issue,” says Charles Fuchs, MD, MPH, director of Dana-Farber Cancer Institute’s Gastrointestinal Cancer Center in Boston, MA. Fuchs helped develop ramucirumab and led REGARD, a phase III trial with results, first reported in 2013, that were key to ramucirumab receiving FDA approval for single-agent use (Lancet 2014;383:31-9).

Ramucirumab is a fully humanized monoclonal antibody that binds to VEGFR-2, a main driver of angiogenesis in tumors, and acts as an antagonist by blocking the VEGFR-2 ligands VEGF-A, VEGF-C, and VEGF-D.

In the REGARD study, two thirds of the 355 participants with inoperable or metastatic advanced stomach cancer or GEJ adenocarcinoma received ramucirumab, and the rest placebo. All had previously received fluoropyrimidine-based or platinum-based chemotherapy. Ramucirumab extended median overall survival (OS) by 1.4 months, and median progression-free survival (PFS) by 0.8 months.

Although these improvements may seem modest, Fuchs points out that the benefit of a new drug in medical oncology is often incremental. He also notes that ramucirumab “offers a superior toxicity profile” compared to standard cytotoxic drugs, with patients tolerating its main side effect, hypertension, very well.

Earlier this year, Lilly Oncology reported results from a second phase III study, RAINBOW, in which 665 patients with metastatic stomach cancer received either ramucirumab plus paclitaxel, or paclitaxel alone. Combination therapy extended median OS by 2.2 months and median PFS by 1.5 months, with patients reporting manageable side effects and improved quality of life.
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