Next-Generation CAR T Cells Counter Exhaustion

T-cell exhaustion continues to limit the long-term durability of cellular immunotherapies. In a new model for studying this mechanism of immune failure in human cells, scientists have discovered a transcription factor that, when overexpressed, helps make chimeric antigen receptor (CAR) T cells resistant to exhaustion (Nature 2019;576:293–300).

The study authors—through their company Lyell Immunopharma—hope the findings will help inspire a new generation of exhaustion-proof adoptive cell therapies for solid tumors. “There certainly are multiple barriers to overcome to get to curative cell therapies for solid tumors, and we believe exhaustion is one of those major barriers,” says Rachel Lynn, PhD, associate director of research at Lyell, who conducted the research at Stanford University School of Medicine in California.

Her team’s new CAR T-cell model “captures some of the downstream biology that’s active in these cells and offers a great way to test new hypotheses so we can eventually make better exhaustion-resistant cells,” she adds.

Working with Crystal Mackall, MD, Lynn and her colleagues had previously engineered a CAR with antigen-independent signaling, but they wanted to boost its activity levels further. So they swapped in a different single-chain variable fragment, while keeping the same hinge and costimulatory domains. In this way, they obtained a receptor that, when transduced into healthy T cells, displayed more severe signs of exhaustion, including increased expression of inhibitory receptors and diminished capacity for cytokine signaling, thereby hastening T-cell dysfunction and impairing antitumor effects.

“There haven’t been good models of human T-cell exhaustion,” notes Mackall, a cofounder of Lyell. “So, we created this reductionist model of exhaustion—which is, by design, all about excess signaling.”

In these cells, the researchers also noticed widespread epigenetic changes, including less densely packed chromatin near exhaustion-associated genes and a surfeit of one particular type of regulatory binding site in those regions. The binding sites corresponded to those for transcription factors of the AP1 family. One, known as c-Jun, helps drive expression of IL2, a cytokine involved in promoting T-cell effector function and keeping exhaustion at bay.

The researchers overexpressed c-Jun in their cells and found it could prevent exhaustion. They tweaked the CAR construct to boost c-Jun activity and observed enhanced expansion potential, improved functional capacity, diminished terminal differentiation, and increased potency against tumor cells with low antigen density. What’s more, the cells displayed greater tumor control in mouse models of leukemia and osteosarcoma, demonstrating that “c-Jun overexpression can enhance the antitumor activity of CAR T cells in the solid-tumor setting,” says Tony Tiganis, PhD, of Monash University and the Peter MacCallum Cancer Centre in Melbourne, Australia.

In the osteosarcoma xenograft model, Lynn says the cancers appeared to be “on their way to full regression,” but her team never tracked the tumors long enough to demonstrate complete clearance, and a propensity for GVHD made it impossible to gather long-term survival data. “By contrast,” Tiganis says, “our studies have shown that deleting PTPN2 in CAR T cells allows for the clearance of antigen-bearing tumors and the marked extension of life span.”

In his latest paper, Tiganis demonstrated that the PTPN2 deficiency enhanced immunosurveillance and CAR T-cell function, allowing mice with implanted breast tumors to live 6 months or longer, instead of dying within 50 days (EMBO J 2019;e103637). He and his colleagues additionally showed that the genetic manipulation promoted recruitment of the CAR T cells to tumors expressing particular chemokines.

“In this way,” Tiganis says, “targeting PTPN2 can overcome key limitations for CAR T-cell therapy, ensuring both homing and sufficient activation of research and development in oncology at AstraZeneca. During a previous 16-year stretch at Gustave Roussy, Soria held various roles, including head of the drug development department, director of the integrated cancer research site, and chief of hospital admissions. He specializes in lung cancer and played a key role in launching early trials of PD-1 and PD-L1 inhibitors.
Novel ADC Solidifies Role in Breast Cancer

Patients with metastatic HER2-positive breast cancer may soon have a new treatment option: the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd; AstraZeneca/Daiichi Sankyo). In a phase II trial, the drug was associated with a high objective response rate (ORR) and a long median progression-free survival (PFS), although some patients developed serious side effects. Results were presented at the 2019 San Antonio Breast Cancer Symposium in Texas, December 10–13, and simultaneously published in The New England Journal of Medicine (N Engl J Med 2019 Dec 11 [Epub ahead of print]).

T-DXd consists of the HER2-targeting monoclonal antibody trastuzumab attached with a cleavable linker to a cytotoxic payload—a topoisomerase I inhibitor derived from exatecan. Ian Krop, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA, who presented the results, highlighted the drug’s distinct features: Its payload is from a class of chemotherapies not typically used in HER2-positive disease, making resistance less likely to have already developed; each antibody carries eight payload molecules, compared with four on the ADC T-DM1 (ado-trastuzumab emtansine, Kadcyla; Genentech); and the payload permeates cell membranes, allowing it to diffuse out of targeted cells and kill neighboring tumor cells.

In a phase I trial, T-DXd elicited an ORR of 59.5% in patients with previously treated advanced HER2-positive breast cancer (Lancet 2019;20:816–26). Now, researchers are reporting on the DESTINY-BREAST01 trial. Patients had received a median of six prior lines of therapy; all had received trastuzumab (Herceptin; Genentech) and T-DM1, and 65.8% had received the HER2 antibody pertuzumab (Perjeta; Genentech). Among 168 evaluable patients, 60.9% responded to the drug and 6% experienced complete responses. The median duration of response was 14.8 months and the median PFS was 16.4 months; the median overall survival was not reached. The drug had similar activity across subgroups, including those with brain metastases. With existing therapies, Krop noted, patients have a median PFS of about 4 to 5 months.

The results are very impressive—if and when this drug becomes approved, I definitely think it will be utilized in patients with metastatic disease,” said Kevin Kalinsky, MD, of the Herbert Irving Comprehensive Cancer Center at Columbia University in New York, NY. However, he underscored the seriousness of ILD. “I think as a field we’ll have to define who’s at risk of developing this, and we’ll have to understand this toxicity in greater depth,” Kalinsky said.

Cesar Santa-Maria, MD, of Johns Hopkins Medicine in Baltimore, MD, considers the toxicity acceptable for metastatic disease, but said it needs to be “ironed out quite thoroughly” before using the drug for earlier-stage disease. He predicted that clinicians will learn to manage ILD as they gain experience with the drug, as they did for cardiac side effects linked to trastuzumab.

Jessica Tao, MD, also of Johns Hopkins, wondered about the efficacy of T-DXd in patients with HER2-low disease—a group ineligible for existing HER2-targeted agents. This question is being explored in a phase III trial.

“Any efficacy seen with this anti-HER2 ADC in the HER2-low cohort would be really exciting,” she said, not only because more patients could benefit, but also because it could “really shape and redefine our definition of what is HER2 positivity.” –Catherine Caruso

Stephen Hahn Confirmed as FDA Commissioner

The U.S. Senate confirmed Stephen Hahn, MD, as the next FDA commissioner in December by a vote of 72–18. The Senate Committee on Health, Education, Labor, and Pensions recommended Hahn’s confirmation following a November hearing during which senators probed his thinking on several issues, notably how the agency would respond to the burgeoning use of electronic cigarettes (e-cigarettes), also known as vaping, and to calls for greater regulation of tobacco in general.

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