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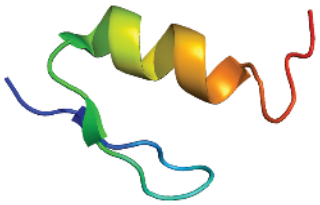

Wilms tumor antigen 1 is overexpressed in AML, making it a promising therapeutic target.

taken from a transplant donor for each recipient with a TCR that recognizes a piece of WT1 presented on the cell surface by MHC molecules.

The substrate cells used to insert the WT1-specific TCR were selected for specificity to Epstein–Barr virus (EBV), as most cells recognizing EBV have central memory characteristics and are predicted to persist. EBV-specific T cells are also less prone to cause graft-versus-host disease (GVHD) than other immune cells, notes Patrick Hanley, PhD, of Children's National Medical Center in Washington, DC, and using them "as the vehicle to deliver the TCR is really creative."

WT1 was chosen as a target because it is overexpressed in AML and other types of cancer. The TCR used in the therapy interacts with HLA-peptide complexes corresponding to the HLA-A*0201 allele present in about half of people of European ancestry.

Clinicians administered the TCR-bearing T cells within a few months of each patient's stem-cell transplant and shortly after tests showed no evidence of residual disease. Infusions were well tolerated, with no toxicity to tissues expressing normal levels of WT1 and no obviously elevated risk for GVHD.

After a median of 44 months, none of the trial participants had relapsed. Based on historical controls, about half would be expected to do so had they not received the TCR therapy.

The high levels of engraftment, persistence of the engineered T cells, and prolonged relapse-free survival point to a "very strong signal" of efficacy, says Aude Chapuis, MD, a co–first author of the study. "If I was a transplant patient," she adds, "you bet I'd want to receive those cells"—at least before a relapse.

As Chapuis reported in July at the American Association for Cancer Research's Immune Cell Therapies for Cancer meeting in San Francisco, CA, the TCR-redirected T cells do not work as well against relapsed AML among patients with detectable disease.

Investigating the causes of failure in this unpublished work, Chapuis and her colleagues found ways to improve the therapy. They now hope to develop a product that engages helper $CD4^+$ T cells alongside $CD8^+$ T cells. Plus, because active leukemic cells had evolved to stop producing the piece of WT1 targeted by JTCR016, they are exploring whether targeting a different section generates better results. "We hope our 2.0 version will be a lot better," Chapuis says. *–Elie Dolgin* ■

New Center Takes Aim at Resistance

The Institute of Cancer Research (ICR) in London, UK, announced the launch of the Centre for Cancer Drug Discovery, which will bring together drug developers and evolutionary biologists to take on one of the biggest challenges in cancer treatment: drug resistance.

"We've made many strides in cancer treatment—we have targeted therapies, we have chemotherapeutics, we're really getting into immuno-oncology—but we know that resistance invariably happens, and then you get relapse," explains Olivia Rossanese, PhD, head of biology in the new Centre for Cancer Drug Discovery. "In a number of cases, that resistance is essentially evolution and adaptation, and the evolution is driven by a Darwinian process."

The center, which has secured more than $62 million in funding thus far, will house the ICR Centre for Evolution and Cancer and the Cancer Therapeutics Unit, together totaling about 280 researchers. "[It's] the physical manifestation of our ambition and our focus to really apply the principles of evolutionary biology and cancer biology, and combine that with our ability to design and develop drugs," says Paul Workman, PhD, chief executive officer of the ICR.

Although the center won't open until April 2020, scientists from both groups are already collaborating to determine the most effective combinations of existing cancer therapies, based on how tumors evolve, and developing drugs to target the evolution of cancer.

One approach for the drug combination studies is evolutionary herding, wherein researchers apply knowledge of how cancer cells evolve in response to different therapies to try to control the cancer's behavior. The idea, Rossanese says, is to thoughtfully sequence drugs and administer combinations "to herd cancer cells through various evolutionary pathways until, eventually, we create a situation that the cancer cells can't adapt to or escape from." This research will involve genomic sequencing to track how cancer cells are evolving over time, as well as artificial intelligence and modeling approaches that predict the trajectory of this evolution, Workman adds.

In addition, rather than stopping the growth of cancer cells, researchers want to develop therapies that halt a cancer's evolution, thus preventing resistance. Ongoing work centers on APOBEC3B, a cytosine deaminase that can mutate DNA. Cancer cells often overexpress APOBEC3B—in fact, the enzyme's mutational signature has been observed in more than half of human cancers—and studies have shown that this overexpression can drive resistance by increasing genomic diversity. Thus, researchers are identifying and developing APOBEC3B inhibitors. "You're not really making a drug against an oncogene target, you're making a drug that you would use alongside other medicines to prevent that adaptation and that evolution, and delay time to resistance," Rossanese says.

Rossanese and Workman hope that these and other projects will lead to treatment strategies that prolong patient responses. "We don't just want to be the team that simply comes up with the next kinase inhibitor or the next MDR modulator, and then sits back and waits for the resistance to develop," Workman says. "Cancer drug resistance is an arms race, and we want to stay ahead of the cancer cells." *–Catherine Caruso* ■

CAR T Cells: Hitting the Pause Button

Researchers have found a way to temporarily halt the action of chimeric antigen receptor (CAR) T cells, if necessary, without compromising therapeutic efficacy. The strategy, involving the small-molecule inhibitor dasatinib (Sprycel; Bristol-Myers Squibb), shows preclinical promise and could eventually help mitigate the therapy's side effects (Sci Transl Med 2019;11:eaau5907).

AACR American Association for Cancer Research

CANCER DISCOVERY

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