

Penn discovers new, rare mechanism for ALL to relapse after CAR T cell therapy

October 1 2018



CAR T Cells ready for infusion. Credit: Penn Medicine

A single leukemia cell, unknowingly engineered with the leukemia-targeting chimeric antigen receptor (CAR) lentivirus and infused back into a patient, was able to reproduce and cause a deadly recurrence of B-

cell acute lymphoblastic leukemia (ALL). New research from the Abramson Cancer Center of the University of Pennsylvania found that in one patient, the CAR lentivirus that would usually enter a T cell to teach it to hunt cancer also ended up binding with a leukemic cell. The presence of the CAR on the leukemic cell may have given that cell the ability to hide from the therapy by masking CD19, the protein that CARs target to kill cancer. Leukemic cells without CD19 are resistant to CAR T therapy, so this single cell led to the patient's relapse. *Nature Medicine* published the findings today.

The treatment, developed by researchers in Penn's Perelman School of Medicine and at Children's Hospital of Philadelphia (CHOP), modifies patients' own immune T cells, which are collected and reprogrammed to potentially seek and destroy the patients' [cancer cells](#). Once they are infused back into patients' bodies, these newly built cells both multiply and attack, targeting cells that express CD19.

"In this case, we found that 100 percent of relapsed leukemic cells carried the CAR that we use to genetically modify T cells," said the study's lead author Marco Ruella, MD, an assistant professor of Hematology-Oncology at Penn. "This is the first time in hundreds of patients treated at Penn and other institutions that we've observed this mechanism of relapse, and it provides important evidence that due to the delicate and complex manufacturing process any slight variation can have an impact on patient outcomes."

The patient, a 20-year-old who received CAR-T cell therapy manufactured by Penn as part of a Penn-sponsored clinical trial which was completed in 2016, entered the trial with very advanced leukemia that had relapsed three times previously. After receiving the modified T cells, the patient had a complete remission for nine months before relapsing. In about 60 percent of ALL relapses, testing shows cancer cells that do not express CD19. CD19 was also not detectable at relapse

in this patient. But in this case, analysis showed the [leukemia cells](#) were positive for the CAR protein.

This study comes on the heels of another case which showed essentially the opposite situation—a patient went into remission thanks to [a single CAR T cell](#) that reproduced and fought off [chronic lymphocytic leukemia](#) (CLL).

"We learn so much from each patient, in both success or failure of this new therapy, that helps us improve these still-developing treatments so they can benefit more patients," said J. Joseph Melenhorst, Ph.D., an associate professor of Pathology and Laboratory Medicine and a member of Penn's Center for Cellular Immunotherapies. Melenhorst was the senior author on this study as well as the research showing remission from a single cell. "This is a single case, but is still incredibly important and can help us refine the intricate processes required for manufacturing CAR-T cell therapy to ensure the best chance of long-term remissions."

More information: Marco Ruella et al, Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell, *Nature Medicine* (2018). [DOI: 10.1038/s41591-018-0201-9](#)

Provided by Perelman School of Medicine at the University of Pennsylvania

Citation: Penn discovers new, rare mechanism for ALL to relapse after CAR T cell therapy (2018, October 1) retrieved 25 April 2024 from <https://medicalxpress.com/news/2018-10-penn-rare-mechanism-relapse-car.html>

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