Chronic lymphocytic leukemia patient goes into remission thanks to single CAR T cell

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Joseph A. Fraietta, Ph.D. (left) and J. Joseph Melenhorst, Ph.D. (right) Credit: Penn Medicine

The doctors who have spent years studying the case call it "a series of fortunate events." What began as a remarkable response to chimeric

antigen receptor (CAR) T cell therapy is now providing evidence about the human genome and immune response that could help turn gene therapy non-responders into responders. Researchers at the University of Pennsylvania's Abramson Cancer Center say a patient treated for chronic lymphocytic leukemia (CLL) in 2013 went into remission because of a single CAR T cell and the cells it produced as it multiplied, and has stayed cancer free in the five years since, with CAR T cells still present in his immune system. The findings, published today in *Nature*, show the response is tied to where the CAR gene inserted itself into the patient's T cell DNA, a key factor that may help improve response rates to the therapy.

CLL is a type of cancer that starts in cells that become certain white blood cells in the bone marrow, and then move into the blood and lymph nodes. These cancer cells reproduce too quickly and crowd out other cells in the bone marrow. They also don't mature properly and thus don't fight off infection as well as they should. The American Cancer Society estimates there will be about 21,000 new CLL cases in 2018 and around 4,500 deaths from the disease. Many of these patients will undergo a bone marrow transplant, but a potential additional treatment is CAR T cell therapy, which involves collecting patients' own immune T cells, reprogramming them to recognize and kill cancer, and then infusing them back into patients' bodies. The approach is approved by the U.S. Food and Drug Administration for certain acute lymphoblastic leukemia patients as well as some non-Hodgkin's lymphoma patients, but is not currently approved for treatment of CLL.

Patients typically receive three consecutive infusions with increasing doses—10 percent, 30 percent, and 60 percent—to control for cytokine release syndrome (CRS). CRS is a common toxicity associated with CAR T therapy and includes varying degrees of flu-like symptoms, with fevers, nausea, and muscle pain, and can require ICU-level care. The patient in this report received the first two infusions of 10 and 30

percent, but did not initially respond. "It wasn't until day 50 that the patient experienced CRS, which indicated the CAR T cells were active and may be having an anti-tumor effect," said the study's senior author J. Joseph Melenhorst, Ph.D., an associate professor of Pathology and Laboratory Medicine in Penn's Perelman School of Medicine and a member of Penn's Center for Cellular Immunotherapies.

Imaging showed the tumor had gotten smaller, so doctors decided to infuse the patient with the final 60 percent. The patient went into remission and has stayed there for five years and counting."It's the outcome we're always hoping for, but we know we can learn so much from every single patient no matter what. We brought this from the bedside back to the bench to understand as much as we could about what happened and why," said study co-senior author Carl June, MD, the Richard W. Vague Professor in Immunotherapy, a professor of Pathology and Laboratory Medicine, and director of the Center for Cellular Immunotherapies.

"The first thing we found was that we could trace the lineage of the patient's CAR T cells back to a single, original cell," said the study's lead author Joseph A. Fraietta, Ph.D., an assistant professor of Pathology and Laboratory Medicine and a member of the Center for Cellular Immunotherapies. "It's a truly remarkable finding, and essentially tells us the minimum dose needed for CAR T cells to do their job is one.

"This patient's CAR T cells were engineered to seek out a protein on leukemia cells known as CD19. In this strategy, the genetic code for the CAR that recognizes CD19 protein is randomly inserted into the patient's DNA by a genetically-modified virus. In this particular case, researchers found the CAR sequence inserted into a gene called TET2 that normally regulates blood cell formation and keeps growth of these cells in check. Once the TET2 gene was disrupted, the single CAR T cell expanded massively and wiped out this patient's leukemia. "Killer T cells

that normally fight off infection generally can't beat cancer alone because they're older, past their prime, and often outnumbered," Fraietta said. "However, younger cells make the difference because of their ability to expand massively into an army of effectors. In this case, they got a chance to do their work because TET2 was inhibited which affected epigenetic pathways to drive this response."

"This analysis required a huge collaboration between immunologists, cell biologists, T cell experts, cancer biologists, and clinicians," Melenhorst said. "Fortunately, we have all of that expertise here, and it proved invaluable."

Other co-authors of the study include Frederic Bushman, Ph.D., the William Maul Measey Professor and chair of Microbiology, Shelley Berger, Ph.D., the Daniel S. Och University Professor and a Penn Integrates Knowledge Professor with appointments in the Perelman School of Medicine's department of Cell and Developmental Biology and the School of Arts and Sciences department of Biology, and David Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in the Abramson Cancer Center.In 2012, Penn and Novartis entered into a global collaboration to further research, develop and commercialize Kymriah, formerly known as CTL019, and other CAR T cell therapies for the treatment of cancers. In August 2017, the U.S. Food and Drug Administration approved Kymriah for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or relapsed. In May of 2018, the approval was expanded to include the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) - the most common form of non-Hodgkin's lymphoma—as well as high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

More information: Joseph A. Fraietta et al, Disruption of TET2

promotes the therapeutic efficacy of CD19-targeted T cells, *Nature* (2018). DOI: 10.1038/s41586-018-0178-z