

Study of decade-long leukemia remissions after Car T reveals new details about persistence of personalized cells

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CLL patient Doug Olson with his children, CAR T cell therapy recipient in remission. Credit: Penn Medicine

In the summer of 2010, Bill Ludwig and Doug Olson were battling an insidious blood cancer called chronic lymphocytic leukemia (CLL). They'd both received numerous treatments, and as remaining options became scarce, they volunteered to become the first participants in a clinical trial of an experimental therapy underway at the Abramson Cancer Center and the Perelman School of Medicine at the University of Pennsylvania. The treatment would eradicate their end-stage leukemia, generate headlines across the globe, and usher in a new era of highly personalized medicine.

Called Chimeric Antigen Receptor (CAR) T cells, these genetically modified tumor-targeting cells are a living drug made for each patient out of their own cells. Today, an analysis of these two patients published in *Nature* from the Penn researchers and colleagues from Children's Hospital of Philadelphia explains the longest persistence of CAR T cell [therapy](#) recorded to date against CLL, and shows that the CAR T cells remained detectable at least a decade after infusion, with sustained remission in both patients.

"This long-term remission is remarkable, and witnessing patients living cancer-free is a testament to the tremendous potency of this "living drug" that works effectively against [cancer cells](#)," said first author J. Joseph Melenhorst, Ph.D., a research professor of Pathology and Laboratory Medicine at Penn. "Witnessing our patients respond well to this innovative cellular therapy makes all of our efforts so worthwhile. being able to give them more time to live and to spend it with loved ones."

CLL, the first cancer in which CAR T cells were studied and used at Penn, is the most common type of leukemia in adults. While treatment of the disease has improved, it remains incurable with standard approaches. Eventually, patients can become resistant to most therapies, and many still die of their disease.

Olson was diagnosed with CLL in 1996 and Ludwig in 2000. By 2010, their cancers had mutated and no longer responded to standard therapy. But as CAR T cell patient pioneers, both achieved complete remission that year. Olson, a former scientist, has taken up distance running and completed six half marathons. He also fundraises for the Leukemia and Lymphoma Society and helps newly diagnosed patients. After his treatment, Ludwig, a retired corrections officer, traveled the country with his wife in a motor home and celebrated milestone events with his family, from holidays to the arrival of new grandchildren. In early 2021, he died due to COVID-19 complications.

While durable remissions have been demonstrated in relapsed, refractory B cell malignancies with CD19-specific CAR T cells, before now, little has been known about the long-term potential and stability of the infused cells. In their latest analysis, the researchers observed an evolution of the CAR T cells over time, with a highly activated CD4+ cell population emerging and becoming dominant in both patients. The data suggest two distinct phases of CAR T-cell therapy responses in these patients with the initial phase dominated by killer T cells, and long term remission controlled by CD4+ T cells. In the ensuing years, these CD4+ cells continued to demonstrate tumor-cell-killing characteristics and ongoing proliferation, which is a hallmark of CAR T cells' efficacy against cancer: its intense ability to survive and thrive inside the body.



First patient treated in study, Bill Ludwig, with Carl June, MD, University of Pennsylvania. Credit: Penn Medicine

The CD4 protein is encoded by the CD4 gene. CD4+ T helper cells are white blood cells that are a vital part of the immune system. In one patient, CD4+ cells made up 97.5 percent of CAR T cells at year 1.4 and then over 99.6 percent from year 3.4 to the latest time point (9.3 years) after infusion. In the second patient, CD4+ cells made up 97.6 percent of CAR T cells 7.2 years after infusion. This surprising finding of CD4+ cell dominance led researchers to rethink the possibility that CD4+ T cells may be primarily responsible for distinguishing T-helper from T-cytotoxic cells.

"CAR T cell therapy has been extremely effective for specific leukemias

and lymphomas, and we look forward to continuing our efforts in these cancers, while also looking at their impact on solid tumors with research in this area to see more development in the coming years," said David L. Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Cell Therapy and Transplantation at Penn. "We often say that we learn something from every patient we treat with these therapies, and Bill and Doug, in particular, have given us so many clues that keep us focused on the next generation of personalized therapies."

"Penn has begun testing next-generation T cells in more blood cancers, including lymphomas, and against the challenging solid tumor cancers," said senior author Carl H. June, MD, the Richard W. Vague Professor in Immunotherapy in Pathology and Laboratory Medicine at Penn and director of the Center for Cellular Immunotherapies and the Parker Institute for Cancer Immunotherapy at the University of Pennsylvania. "A considerable amount of deep learning goes into studies that will fine tune the way cancer patients are treated with CAR T [cells](#), and we look forward to the next phase of research and enhancements, including how best to use this approach to target other cancers and diseases."

More information: J. Joseph Melenhorst, Decade-long leukemia remissions with persistence of CD4+ CAR T-cells, *Nature* (2022). [DOI: 10.1038/s41586-021-04390-6](https://doi.org/10.1038/s41586-021-04390-6).
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