Q&A: Carl June on CAR T-cell Therapy

Engineered T cells have the potential to become first-line cancer therapies across the globe

The first-approved living drugs, chimeric antigen receptor (CAR) T-cell therapies have shown unprecedented efficacy against several hematologic malignancies. “CAR T-cell therapy is going to spread,” says Carl June, MD. Over 30 years of research, June has characterized fundamental properties of T cells, which he then harnessed for T-cell engineering, and turned those engineered T cells into therapies that are active in blood cancers. He now engineers T cells targeting other malignant and chronic diseases at the University of Pennsylvania, where he also directs the Center for Cellular Immunotherapies at the Perelman School of Medicine and director of the Parker Institute for Cancer Immunotherapy. June was ranked 7th among the top 100 most important people in the world according to TIME magazine in 2018. The person who nominated him was Emily Whitehead, the first pediatric patient treated with CAR T cells, whose headline-making recovery story brought CAR T-cell therapy to public recognition. He spoke with Blood Cancer Discovery’s Tanya Bondar about the past, present and future of CAR T-cell cancer therapies.

In your TED talk, you say, “Discoveries of this magnitude don’t happen overnight.” What went into making T-cell engineering a clinical triumph?

It was a journey. Initially, even though I was trained as a leukemia specialist, I worked on AIDS for 10 years with Jim Riley, PhD, and Bruce Levine, PhD, and we learned a lot about vector engineering. Our first CAR T cells were to treat patients with AIDS. Then we started doing leukemia research, so the goal changed. You apply what you learn and then bolt that onto something else. We had to have different innovative solutions, like how to genetically modify cells efficiently. It turned out that HIV was really good for this. We had to make a robust culture system for T cells. And we had to learn how to engineer them. When we found out that the 4-1BB signaling domain had a big effect on cell persistence, this piece in with the other things. Finally, all the little parts came together. And they actually worked better in humans than in mice.

Why do you think the approach worked better in humans?

Human T cells are more robust as they have to survive our entire lives. The mouse has ongoing thymopoiesis its whole life, so it doesn’t need to make robust T cells that are energetically demanding from an evolutionary perspective. I think that’s why human T cells are much more effective than mouse T cells engineered with the same CAR.

Your focus shifted from HIV to cancer immunotherapy when your first wife was fighting cancer. Did that experience change the way you do research?

Her illness made me realize that I needed to focus on getting things into the clinic. I learned how hard it is to do translational research, to put together the regulatory protocols to get in place all the parts owned by different companies. And that’s probably why our CAR T-cell trial was the first to garner FDA approval.

How do you see the role of academia versus industry in innovative therapies?

It depends on the kind of medicine being developed. With pharmacologic targeted therapies, it used to be a one-way handoff from academia to pharma, as pharma is really good at medicinal chemistry. The cell therapies are turning out to be very different. The academic centers like Baylor, St. Jude, Fred Hutchinson, MSKCC, and Penn have established biotech and regulatory support to start new CAR trials right at the university. And it’s faster and cheaper than if biotech or big pharma does it. Second, to develop new CAR T-cell therapies, you need to be where the patients are. You have to get samples from patients after the infusion to figure out if it’s working. It’s hard for the pharmaceutical industry to do that with central manufacturing. I think next-generation cell therapies will be done in partnerships with academia and biopharma with continuous improvement. Another issue with pharma is that the appetite for innovation is increased when their patent protection runs out. But for CAR T cells, patent duration probably doesn’t matter, as their development cycle is faster than that of new small-molecule therapies. CAR T cells can go from a finding in a mouse to a clinical trial in a year, something not possible with small molecules.

Why is translation to the clinic faster for CAR T cells than for standard drugs?

Of the thousands of people treated with CAR T cells, not once have the cells transformed. So the FDA is now comfortable with autologous T-cell therapies. Even if you build on a current CAR T, with a new CAR signaling domain for example, it’s still a primary human T cell and can go straight from mice to humans without a need to test in non-human primates. That’s an advantage that makers of other drugs don’t have.
How many people have lived longer thanks to CAR T-cell therapies?

The numbers are in the thousands, but we don’t know the precise answer because many of the patients are in China. And many of these patients are children so they have more years to live than elderly adult patients. The first checkpoint therapy was approved in 2010, and now there have been over a million people treated. CAR T cells were approved in 2017 and so are at least seven years behind. We can look forward to CAR T cells going that same sort of trajectory. There’s now more than 500 registered CAR T-cell clinical trials and it’s on a similar exponential upswing that checkpoint therapies experienced beginning in 2010.

Do you expect this trajectory even though CAR T cells are not as easy to make as traditional medicines?

The current leukemia therapy in developed countries involves 3 years of radiation and chemotherapies, requiring lots of lab and hospital visits. Logistically, a one-time cell therapy treatment would be better in low- and middle-income countries. Middle-income countries may leapfrog to CAR T cells, like when Africa went to mobile phones, skipping landlines.

How can developing countries leapfrog to CAR T-cell therapies?

I’ve been privileged to work on two projects toward this goal. One is in Costa Rica, which has a population of 5 million. They have uniform health care, and all children with cancer are treated at one hospital. We have been working on this project with Dr. Stephen Grupp at Children’s Hospital of Philadelphia. The first children will come to the United States, where their cells will be collected by apheresis and manufactured into CAR T cells. Then the children will be flown home, and then the cells will be sent to their hospital to be reinfused. We’re trying to do the same in India, a country with 1.3 billion people and not a single CAR T-cell trial. We’re working with Kiran Mazumdar’s Medical Foundation cancer care center in Bangalore to manufacture CAR T cells locally for the people there. CAR T-cell therapy is going to spread.

Did the COVID-19 pandemic place your research on pause?

We are allowed to treat patients in our cancer trial center, and our CAR T-cell manufacturing group is up and running. But there’s an Achilles’ heel there: to do phase I trials, we need to study the responses through biopsies, which currently cannot be processed during the lockdown. So it becomes unethical to treat patients, if you can’t do the study as you said you would in the protocol: does it work or not? does it cause toxicity? In regulatory terms, we have “paused” the trials until we think it’s safe to resume. And as our mouse colony was culled, we have very few experiments ongoing. It’s been really frustrating that the infrastructure is not intact enough to continue the research. We are excited to begin reopening our labs in the coming months.

How do your trainees stay productive during this time?

It’s very sad. Most young postdocs and graduate students have almost no risk if they get infected, so they’re sacrificing part of their career for the older people like me who are at higher risk. It’s ethically debatable, how long that can go on. For graduate students rotating in my lab, the timing worked out so that they didn’t get to do a single experiment in the lab. So instead, they have written review articles with me. At least that way they have something to show on their CV. I’m really worried about how the cutback in science funding due to COVID-19 will impact graduate students. Many of them could be forced out of science, as happened in the 2008 recession. So we all have to lobby that we don’t lose people in science because of the economic consequences of COVID-19.

What do you think will be the next revolution in this field?

I think one would be scientific and the other engineering. The scientific one is to engineer cells with potent activity in solid cancers. With all CARs approved or being tested, we will have effective therapies for almost all blood cancers in the next 5 years. However, blood cancers account for about 10% of all cancers in the United States. Solid tumors are complex, but I’m confident that the field will make CARs to treat them. That will be a huge breakthrough.

The other part is for CAR T cells to go into community hospitals. Right now, Novartis is using a complex manufacturing process that Bruce Levine established in my lab in 1992, and logistically, they transport cells around the world to meet the demand. In the future, I think there’ll be little boxes that you could put in each big hospital, at the point of service. You draw blood from a patient, insert it into that little box, and then several days later out comes CAR T cells. That will make a huge difference on whether it can be used as first-line therapy. And that will happen. I promise you that cell engineering in a box is doable!
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