Q&A: Expert discusses the 'boundless potential' of CAR T cell therapy

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Carl June, at the flash mob celebration of the FDA approval of the CAR T cell therapy he developed, in August 2017. Credit: Penn Medicine Magazine

For most of modern medicine, cancer drugs have been developed the same way: by designing molecules to treat diseased cells. With the advent of immunotherapy, that changed. For the first time, scientists

engineered patients' own immune systems to recognize and attack diseased cells.

One of the best examples of this pioneering type of medicine is CAR T cell therapy. Invented in the Perelman School of Medicine by Carl June, the Richard W. Vague Professor in Immunotherapy, CAR T cell therapy works by collecting T cells from a patient, modifying those cells in the lab so that they are designed to destroy cancerous cells, and reinfusing them into the patient.

June's research led to the first FDA approval for this type of therapy, in 2017. Six different CAR T cell therapies are now approved to treat various types of blood cancers.

CAR T cell therapy holds the potential to help millions more patients—if it can be successfully translated to other conditions. June and colleagues, including Daniel Baker, a fourth-year doctoral student in the Cell and Molecular Biology department, discuss this potential in a perspective published in *Nature*.

As research at Penn and elsewhere moves into early-stage clinical trials, it's no longer just a theoretical possibility: CAR T cell therapy is making waves in solid tumor cancer types and even beyond cancer, for other diseases. Here, June and Baker, a member of June's lab, explain how.

CAR T cell therapy is described as a 'living drug.' What does that mean?

June: CAR T cells are derived from our own immune system. T cells are a type of white blood cell that give our bodies lifelong memory to infections. CAR T takes those immune cells and makes them cancer killers. The cells divide when they find their targets; a single cell can turn

into a billion cells, so you can make an entire army of cancer killers from one cell. All the cells— and all their descendants— are identical.

We found that the CAR T cells survived in some of the first patients treated—back in 2010—for more than a decade. So, we can really say CAR T cells are a living drug. CAR T cell therapy has exquisite selectivity for blood cancers— meaning it does a good job of only attacking cancer cells— and because it doesn't affect healthy cells, it doesn't cause the same side effects chemotherapy does. That that's been a major paradigm shift.

What other diseases do researchers think CAR T cell therapy could be effective for and why?

June: CAR T cell therapy has been remarkably successful for blood cancers like leukemias and lymphomas. There's a lot of work happening here at Penn and elsewhere to push it to other blood cancers and to earlier stage disease, so patients don't have to go through chemo first. Another big priority is patients with solid tumors because they make up the vast majority of cancer patients.

Beyond cancer, we're seeing early signs that CAR T cell therapy could work in autoimmune diseases, like lupus. In lupus, immune cells target the patient's own DNA, creating antibodies against their DNA, which leads to tissue damage. CAR T cell therapy could be used to target the cells that make those autoimmune antibodies and kill them, which should resolve the tissue damage. And that's exactly what the early trials are showing.

Essentially it boils down to two questions: Can we identify a population of cells that are bad? And can we target them specifically? Whether that's asthma or chronic diseases or lupus, if you can find a bad

population of cells and get rid of them, then CAR T cells could be therapeutic in that context.

Baker: What's exciting is it's not just theoretical at this point. There have been clinical reports in other autoimmune diseases, including myasthenia gravis and inflammatory myopathy. It's still early, and we're not going to know for a while whether these are curative, or what the long-term effects are going to be.

But we are seeing early evidence that CAR T cell therapy will be successful beyond cancer. And it's really opening the minds of people in the field to think about how else we could use CAR T. For example, there's some pioneering work at Penn from the Epstein lab for heart failure. The idea is that you could use CAR T cells to get rid of fibrotic tissue after a cardiac injury, and potentially restore the damage following a heart attack.

What's the status of research into CAR T cell therapy for solid tumors and other, non-cancer diseases?

June: I think we're going to see rapid progress in cell therapy research now that infrastructure is established. We must avoid over-hyping how fast this can happen because clinical research always takes longer than we would like, especially when it's not in immediately lethal diseases, like cancer. When we began clinical trials with leukemia patients back in 2010, their life expectancy was measured in weeks and months. So, it didn't take long to follow up and see that CAR T cell therapy had real benefit.

But when you look at diseases that can take years to get proof that you have efficacy, then the clinical trials take longer. Just as in cancer, we'll have to start off with patients at the most critical stage of disease, where

there are no other potential therapies. While earlier stage disease may ultimately be the better place to implement these therapies, we have to begin clinical trials in late-stage disease.

So, it will take longer than it did for leukemia, but I think the advantage now is that it's going to be a broad research effort between academia and biopharma industries.

How would CAR T cell therapy—or other forms of cell therapy—work differently when treating an illness that's not cancer?

Baker: The basic mechanism is the same: a CAR T cell is going to identify and kill bad cells. But there are some potential advantages: Cancer is a really difficult, rapidly mutating disease, with what we call a high disease burden. In the first patients that were treated with CAR T cell therapy, pounds of tumors cells were eliminated.

In most other diseases, that's not the case. Patients with autoimmune disease or heart disease don't have pounds of diseased cells to eliminate, so theoretically, you may need fewer T cells. One of the challenges with using CAR T cell therapy for solid tumors is the dense, immunosuppressive tumor microenvironment.

Most other diseases don't have their cells hiding in places that are so hard for the immune system to reach. And the hallmark of cancer is that it's constantly changing—or mutating—which isn't the case for most other diseases. The fact that CAR T cell therapy has worked so well under such difficult circumstances makes the idea of using it in other settings all the more promising.

June: While it may seem counterintuitive, it may be easier to use CAR T cell therapy to treat other diseases, than to treat cancer.

What are some of the current limitations of CAR T cell therapy and solutions to make it more accessible for patients?

June: I'd put the current limitations into two main baskets: One is scientific knowledge. And the other is really an engineering issue of scaling out manufacturing access so that it's accessible to more patients.

The science is rapidly being solved. Back when we started, there were less than a handful of groups working on CAR T in the entire world. Now, thousands of laboratories are working on this. While the science is most effectively addressed in academic settings, where innovation occurs more rapidly, the progress on manufacturing is happening primarily within the biopharma industry.

CAR T cells are currently made using the process we developed in the 1990s. It was an academic process that was not designed to be brought to scale. It's heavily dependent on highly trained scientists and technicians, so there's a workforce limitation to meet the demand for therapy. One obvious solution is automation. The biopharma industry is working to make "plug and play" instruments that would take blood from the patient and manufacture the CAR T cells in an automated fashion, without the need for human intervention.

Also, for any new paradigm-shifting therapy, you have to train the physicians and nurses on how to deliver it efficiently. It usually takes about a decade to transfer that level of knowledge from major cancer centers out to more rural areas. We're in the midst of that right now with CAR T cell therapy. Clinicians also get better at treating side effects from new therapies over time.

In the early days of our CAR T cell clinical trials, 20–30% of patients

would have to go to the ICU to treat cytokine release syndrome (CRS), a side effect that happens when the immune system overreacts. Now, it's much less because clinicians have learned how to treat it.

Finally, the workforce is now hiring many more people to work on cell therapy. I've had 55 grad students in my lab since coming to Penn. When we started in 1999, if people asked about coming to my lab to work on CAR T cells, others in the field would tell them not to because it was just an academic curiosity. There was no industry or pipeline of jobs, and now that's completely changed. Now this field is attracting many young talented trainees such as Daniel, who are really increasing the pace of innovation this area.

What made you interested in studying CAR T cell therapy, and what research questions do you hope to explore in your career?

Baker: I was in high school when the first patients were treated with CAR T cells. I was totally unaware of all the work going on! When I came to Penn, it just so happened that my path crossed with Jon Epstein,MD [Penn Medicine's chief scientific officer].

That's how I learned about the pioneering discoveries in CAR T cell therapy happening here. I came across Carl's TED Talk, and when I heard the stories about giving those patients back their lives, I found it really inspiring. I thought it would be exciting to be somewhere and do something that could truly change people's lives. That's why we do science—to help people—and that was one of the reasons why I pursued the field of cell therapy.

There's no question that over the last decade, CAR T cell therapy has revolutionized cancer. Being given the freedom by Carl, Zolt, and other

mentors to explore broadly and ask the question of whether CAR T can work elsewhere—like chronic diseases or aging—and design an ambitious project to find out is something unique to the atmosphere at Penn.

I'm hoping to play a role in bringing these next generation therapies to patients and make a real impact over the next decade. I think there's potential for cell therapy to be a new pillar of medicine at large, and not just a new pillar of oncology!

It took decades of research to get FDA approval for the first CAR T cell therapy. When did you first begin to realize the enormous potential of CAR T, and where do you think the field will be in another 20 years?

June: I had a very clear 'aha moment' in 2006 when I thought CAR T cell therapy might work. One of the postdocs in my lab (Carmine Carpenito, Ph.D.) burst into my office with the results of an experiment. He looked at the spleen—which is the organ where a lot of T cells live—of a mouse model and found over half of the cells were the CAR T cells we had injected six months earlier. Those cells had formed long-term memory and cured the leukemia. When I saw that, it made me excited at the prospect that these cells might actually work in humans.

Still, I had real doubt as to whether CAR T cells could work in a complex human autoimmune disease like lupus. I was completely astonished when reports started showing up last year that a single infusion of CAR T cells gave people with lupus drug-free remissions, which no other drug has ever done.

Looking ahead, there will be a lot of cell therapy work in autoimmune

disease, regenerative medicine, aging diseases, and even dementia and infectious diseases. We've already seen several studies for autoimmune diseases get started in a very short period of time. I think in the next couple of decades, we'll continue to see progress in CAR T cell therapy for more cancer types—and see exponentially more clinical trials coming on board for these other disease areas.

It's important to remember that this progress hasn't happened by accident. I want to acknowledge the amazing team of scientists, nurses, and physicians here at Penn Medicine that allowed this research to happen.

The University of Pennsylvania developed a strategic plan in the 1990s to make Penn a hub for cell and gene therapy, and that early investment is why we now have this large infrastructure and talent in Philadelphia for cell and gene therapy. Supporting science is essential to make future cures possible.

More information: Daniel J. Baker et al, CAR T therapy beyond cancer: the evolution of a living drug, *Nature* (2023). DOI: 10.1038/s41586-023-06243-w

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