INTERVIEW

Prof. Carl June: unlocking the potential of T-cell therapies

Prof. Carl June is the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine. He is currently Director of Translational Research at the Abramson Cancer Center at the University of Pennsylvania and is an Investigator of the Abramson Family Cancer Research Institute. He is a graduate of the Naval Academy in Annapolis, and Baylor College of Medicine in Houston 1979. He maintains a research laboratory that studies various mechanisms of lymphocyte activation that relate to immune tolerance and adoptive immunotherapy for cancer and chronic infection. He has published more than 300 articles and is the recipient of numerous prizes and honors, including election to the Institute of Medicine and the American Academy of Arts and Sciences.

Q It would be great if initially you could provide us with your insight into the rationale for using T cells as therapies

There's a lot of rationale now but for me the initial attraction was the results from bone marrow transplants and that's what led me to train in leukemia. The initial bone marrow transplants – usually from a brother or sister – were thought to work as a stem cell rescue following high-dose chemotherapy. The patient would receive super lethal doses of chemotherapy in the hope of eradicating the leukemia, having previously tried lower doses that were insufficient, and this would be followed by the new bone marrow transplant. In some cases this resulted in cures and at the time it was assumed that the dose escalation of chemotherapy was the underlying reason for these responses.

In leukemia, following a bone marrow transplant, if the patient doesn't relapse within around 2 years, they are essentially cured. However, it was eventually discovered that these durable remissions were not due to the chemotherapy dose but in fact it was the impact of the incoming new immune system i.e., the T cells from the brother/sister donor. That was the first human data showing the potent effects of T cell immune therapy and, in this case, given through bone marrow transplant.

Q It's evident we are now entering a new era in cancer care with some truly transformative and potentially curative CAR T-cell therapies. Was there a definitive moment when you stepped back and realized that CAR T cells were a real game changer?

I have worked in this field this for a long time and in fact our first CAR T-cell trial started in 1997 for patients who had HIV. It wasn't until 2010 that we were able to treat our first leukemia patients with the CAR that we are presently using. We clearly had an 'ah-ha' moment after the first three patients, because all three had a striking response.

With the first patient, we weren't sure what was happening – initially he got very sick. He was already in the intensive care unit at the time we treated him and we thought perhaps he had picked up an infection, but all cultures were clear. It turned out he was experiencing tumor lysis syndrome and cytokine release syndrome, which present with a high fever resulting from the tumor being killed by the immune system. So when three patients in a row demonstrated that same reaction following treatment with CARs, we knew we had something that worked.

Q Is it your hope and expectation that this therapeutic approach will eventually become a first-line treatment?

Absolutely, that would be our hope. Right now cancer treatments are given on a first-, second- and third-line basis and when testing a new drug or therapy in humans you are only able to do so in patients who have failed to respond to these approved drugs. Our initial trial is in those patients whose disease has progressed on all other therapies and they have no curative options left. The next step will be to conduct randomized trials in order to move this treatment approach more upfront and actually it's likely that CAR T-cell therapy should actually work better. The patient's immune system is sometimes damaged after receiving several doses of chemotherapy so if CAR T-cell therapy is introduced earlier in their treatment regimen then hopefully we will see even better responses.

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Q Whilst we've seen some remarakable data in leukemia patients receiving CD19 CAR T cells, some patients do not respond. Do you have an understanding of the underlying reasons for partial and non-response?

We now know that this is disease specific and anyone who knows the complexity of cancer would not be surprised to hear this. The mechanisms of resistance are different in chronic leukemia than they are in acute leukemia. Acute leukemia originates closer to the stem cell and it's not uncommon to observe what we call target loss in these patients. In fact that is what we have seen in some of our CD19 acute leukemia patients – when the leukemia comes back, it no longer has CD19.

In our animal models, there's a relatively easy approach to overcome that target loss and that's combining CARs so that the immune escape won't happen. This is very similar to other scenarios whereby combinations of antibiotics for example are given to prevent the aberrance of resistant strains.

Q Can you tell us a little more about the side effects you are seeing in patients and how you're attempting to manage them?

First it's important to distinguish between cytokine storms and cytokine release syndrome. A cytokine storm is the result of the immune system being activated in a non-specific way and can happen within 15 minutes after a potent immune-activating agent is given. Cytokine release syndrome – what we're seeing in patients receiving CAR T therapy – is not disorganized activation of the immune system but is actually targeted. It can take anything from 3 or 4 days up to 2 months for this reaction to happen and is directly associated with the tumor being eliminated. It's very easy to diagnose: patients develop a fever that can range from moderate flu-like up to 106F that is not caused by infection but by the activated immune system. This only happens in our responding patients.

Q And why do you think we are not seeing that in non-responders?

What we've recently discovered and that we can analyze in more than just a handful of patients, is that two factors correlate with a patient response.

First, there's proliferation of the CAR T cells in the patients, which really serves to demonstrate that these are living drugs. In patients who respond the T cells have undergone a lot of proliferation – thousands of times; whereas in the patients who fail to respond we can find CAR T cells but they are not dividing.

The second aspect is that these cells persist. What correlates as a predictive biomarker of response is sustained engraftment of these CARs whereby we can find them in the blood and bone marrow of responding patients.

Q Following on from the amazing results in leukemia, the next big question is whether we can see comparable results in solid tumors. What are the biggest challenges in applying CAR T-cell therapy to solid tumors?

Solid tumors are certainly more complex. The genetics community have sequenced solid tumors and have shown that, for instance in colorectal cancer, it may take 15 years for that tumor to develop and during that time it accumulates sequences of mutations.

This is in contrast to what's been found in leukemia where we see that bone marrow cancers often have very few mutations and are therefore genetically more homogenous. As solid tumors are likely to have many sub-clones present when a patient is first treated, it is therefore more likely that they'll have a resistant cell *de novo*. So that immediately presents a challenge.

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Another aspect is that solid tumors might be sheathed in a scar-like material. For example pancreatic cancer is termed a serous tumor by anatomic pathologists, literally meaning 'scar', because they often feel rocky due to the layers of scar-like tissue. It doesn't take a lot to expect that this type of tumor will be harder for the immune system to access given that is sheathed in a hard firm scar. Therefore in these instances injecting T cells directly into the tumor where the blood supply is limiting might be necessary.

Q Leukemia is a relatively rare cancer compared to some of the solid tumors you are looking at, such as lung and breast. What do you see as the biggest hurdles to getting cell therapies into routine clinical practice for commonly occuring solid tumors?

Initially the challenge was in scientific development: making a CAR cell that could work and elicit a response. Now that's happened, I think there will be many generations in the product life cycle whereby the products will continue to improve and become more sophisticated.

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The big issue facing the routine use of T-cell therapies in more common tumors is engineering – the industry is having to learn how to grow cells in a cost-effective way. At this point, the technology is not available to treat various common cancers because the manufacturing and engineering has not been done.

Only now is there an effort in the industry to make robotics and automated assembly. We recently wrote a review to highlight this issue, using the analogy with the automobile industry. Those kinds of cars were initially made one by one before the development of the much more efficient assembly lines whereby instead of requiring biomechanics to assemble each car they are now produced mostly by robotics. More than 80% of a car is made without human hands touching it and that's what we'll need for CAR T cells.

Q With huge interest from Big Pharma and Biotech we are clearly moving towards the commericialization of T-cell therapies - do you think the industry is equipped for the challenges ahead?

I think we are in the early days of a new industry. When the first monoclonal antibody was made in the UK, you had to grow them in mice to make the so called hybrid technology before they were then harvested. People said it would never be possible to treat humans with antibodies because it was too expensive to grow them. Then the biotechnology revolution happened and it's a matter of history that it's now cheap to make antibodies that are no longer made in mice but in thousand-liter batches and using bioculture technology. I think the same thing will happen with these kinds of cell therapies. The industry will learn and whilst it's going to be a big challenge, I've no doubt it will become efficient in ways we can't even imagine at this point.

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Q You've mentioned that the next few years will see iterative improvements in T-cell therapies – what do you think is on the horizon for next-generation CAR T therapies?

There will definitely be improvements in the way these cells are designed. For example, at the moment we have what we call on-CARs, meaning they are always on, always expressed in the cell.

I think we will get to a point where they're not always on and they will be controllable, so the physician will be able to turn them on or

off at will, perhaps using small molecules or drugs to control them in much the same was as our natural genes are regulated.

To circumvent tumor escape, I believe we will have a combination approach targeting several different molecules on the tumor. So we'll have combinatorial approaches and cells that can be made smart that way.

I started as a fellow training in leukemia in 1983, in the very early days of bone marrow transplantation and I've just returned from a meeting in Parma, Italy where 30 years later, they are doing still more research on how to refine bone marrow transplantation in ways we never thought were possible in 1983. I think 30 years from now we'll be making more and more sophisticated CARs and the technology will be very advanced in ways that we can't predict at this point.

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