What's Next for T-cell Therapies: Q&A with Dr. Stanley Riddell

After approval of the latest cellular therapy for non-Hodgkin lymphoma, the big challenge is how to extend it to common solid tumors.

February 11, 2021 By Sabin Russell

Today's Food and Drug Administration approval of Bristol Myers Squibb's liso-cel for the treatment of non-Hodgkin lymphoma is a milestone in the development of T-cell therapies as potential cures for cancer.

Dr. Stanley Riddell, an immunologist at Fred Hutchinson Cancer Research Center, carried out early CAR T-cell research that contributed to the development of this "living drug," made by genetically engineering the patient's own immune cells to target malignant blood cells.

That technology was first licensed to Hutch spinoff Juno Therapeutics, now a Bristol Myers Squibb company. A Fred Hutch statement regarding the FDA decision is available here.

Prior to that decision, we sat down to talk with Riddell, who recently moved his lab to the Steam Plant, the Hutch's newest research facility, where he continues to look for ways to improve immunotherapies. Below are excerpts of that interview, edited for brevity and clarity, on the next generation of T-cell therapies.

Q: Now that this technology has led to an FDA-approved drug, what lies ahead for CAR T-cell therapy research?

A: I think the trials going on in multiple myeloma are very promising, and I think that that's going to be the next disease for which CAR T cells are going to have an impact and are likely to get approved in 2021. Once it is approved, the field will have to determine how do we best position the therapy to benefit the most patients. We have a large grant at the Hutch with Drs. Geoffrey Hill and Damian Green, as well as investigators at Emory University, to develop next generation approaches in multiple myeloma.

Q: What about further down the road?

A: For these new therapies for blood cancers, there are still patients that either don't respond, or that respond initially and then relapse. We are working on understanding what underlies these

incomplete responses. I think the current data is pointing in a couple of directions where we can improve this therapy.

The first is the quality of the cells. When we manufacture these cells, we have to take them from the patient, engineer them with the chimeric antigen receptor and give them back to the patient. All T cells aren't equal, and work we've done in the lab is to identify the subsets of T cells that are most effective in immunotherapy. A lot of previous chemotherapy damages the immune systems and may affect the ability to develop a highly effective product.

The second problem in blood cancers is that sometimes the cancer can escape because it loses expression of the antigen that we are targeting with engineered T cells. [Antigens are telltale proteins that are expressed, or displayed, on the surface of tumor cells, and are typically the targets that T cells home in on.]

If you're targeting a single molecule on a tumor, especially when there may be billions of cancer cells in the patient, it's possible that some of them will have mutated to lose the target, what we call antigen escape. We're working on a variety of strategies to overcome this problem. We've been designing receptors that would simultaneously target two or even three molecules and have improved sensitivity for cancer cells that express very low levels of antigen.

The third area is the tumor microenvironment. In some blood cancers like lymphoma, these T cells have to go into the bulky tumors and function in that environment. And that can be hostile, both because essential nutrients are consumed by the tumor and not available for the T cells or because the tumors have recruited suppressive cells that inhibit T-cell function.

A fourth area in blood cancers is: How do we bring these therapies earlier in the course of the treatment? Right now we've been treating patients after all conventional therapies and transplants have failed. Ideally, we'd use T-cell therapies much earlier in the course of treatments, and clinical trials to test this are in progress.

Finally, the big challenge is how do we extend T-cell therapy to common solid tumors like breast cancer, ovarian cancer, lung cancer, and pancreatic cancer? We've done work in our lab to identify targets and on how to engineer T cells that are best suited to deal with those types of tumors. There's a lot of work going on by many investigators at Fred Hutch to identify T-cell receptors for antigens expressed by solid tumors, and several of these are moving into clinical testing. We haven't yet seen as dramatic benefits as we've seen the blood cancers, but I think there's every reason to hope that we can engineer these cells in ways that would make them highly functional. I'm optimistic that within the next five years, and hopefully sooner, we're going to see major advances in that area.

Q: Does Fred Hutch in particular have unique tools and skill sets to get us there?

A: It all starts with the science, and I think we are very well-positioned at Fred Hutch with outstanding scientists. The second thing is the infrastructure, and the Hutch has made a strong commitment to immunotherapy, which really evolved out of our bone marrow transplant program.

We developed specialized manufacturing facilities to engineer T cells for safe administration to patients. We've made a commitment clinically, through the formation of the Bezos Family Immunotherapy Clinic, which was specifically designed to test cell-based therapies in cancer patients. Dr. David Maloney, the medical director, has built an incredible team of physicians, nurses and data managers that allow us to do these sophisticated trials and learn from them.

I want to emphasize that Fred Hutch has some of the best scientists in the world. I'm not just talking about the immunology group. We have fantastic basic scientists, tumor cell biologists, and computational biologists. The creation of the Immunotherapy Integrated Research Center is bringing together scientists from all of these disciplines to develop improved immunotherapies.

Q: Right now, you are sitting in a new lab at the Steam Plant. What does that new locale do for your efforts?

Well, I am a very strong believer in the need to build teams to tackle really difficult scientific problems. It wasn't always that way in science. When I started out, you could have your own little lab and work largely in isolation. But now that technologies are so complex and diverse, it's really hard for a single lab to be master of all of these and remain at the forefront of the knowledge that's being created in the field. So bringing scientists together is really important.

The environment in which you bring scientists together is also important. The Steam Plant was designed in many ways to bring together groups of scientists working in transplantation, tumor immunology, cell-based therapy, gene therapy and computational biology in open labs. And all of these disciplines are critically important. I think this environment is visionary.

People often talk about ideas and collaborations that begin at the coffee stand, over a beer or in a social environment. If you go to work and close your office door, you are closing yourself out from information and interactions with your colleagues that can help your research. The Steam Plant is designed to promote interactions between faculty, postdoctoral scientists and students across disciplines. I believe that this will be the key to new discoveries.

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