Q&A: When will patients see personalized cancer vaccines?

April 16 2024, by Alvin Powell

Catherine Wu. Credit: Stephanie Mitchell

Catherine Wu has been a pioneer in a promising approach to fight cancer: vaccines that target specific immune-stimulating molecules, known as immunogenic peptides, generated by the distinct genetic

mutations of any individual cancer.

Wu, Harvard Medical School professor of medicine and Lavine Family Chair for Preventative Cancer Therapies at Dana-Farber Cancer Institute, was honored in February with the $1 million Sjöberg Prize, given for cancer research.

She spoke with The Harvard Gazette about cancer vaccine technology, its promise, and expectations that patients might see it in the near future.

What is a cancer vaccine?

A cancer vaccine aims to vaccinate the individual against immune determinants present in cancer cells to mount an immune response—and hopefully eliminate those cancer cells.

In general, cancer vaccines are therapeutic vaccines, meaning that they are treating an existing cancer, as opposed to a prophylactic vaccine, which is what we typically imagine when we think about vaccines against infectious pathogens.

So, a major goal of a cancer vaccine is to drive the generation and expansion of an army of T cells that specifically recognizes tumor cells and to carry a program to eradicate that cancer. The concept of cancer vaccines has been around for decades, but until only recently, its clinical development has been quite a roller coaster.

You're talking about how the vaccines get around a hurdle in convincing our immune systems to attack cancer cells: The immune system is designed to attack things that are foreign to the body, whereas cancer

cells—though harmful—come out of our own tissues. The immune system doesn't attack because it recognizes tumors as 'us.' Is that right?

Exactly. This is a major challenge for cancer vaccines. Our innovation is that we were among the first to identify tumor-specific peptides that are recognized by the immune system—so-called antigens—through genomic approaches. These "neoantigens" originate from cancer mutations.

Since neoantigens have exquisite restriction of their expression to tumor cells, these would be optimal cancer antigens to go after, setting up the possibility of specific targeting of the cancer cell and not normal tissue. However, a long-existing problem was always the understanding that these neoantigens would differ from individual to individual and thus the conundrum of how one could feasibly go about identifying them on a person-by-person basis.

How did sequencing technology make the difference?

The availability of next-generation sequencing over the past decade has provided time and cost advantages for the DNA and RNA sequencing of cancer samples such that we've been able to sequence thousands upon thousands of cancers. That has given us the stark realization of the vast molecular heterogeneity from tumor to tumor, even among patients with the same type of cancer.

This fact really brings home the idea that a one-size-fits-all approach to cancer treatment or immunotherapy has its limitations. The ability to readily scan cancer genomes through such technology has made it possible to directly find the mutational profile of each cancer and then to identify those mutations that have the potential to generate neoantigens.

Once we realized that it was possible to systematically identify neoantigens from cancer sequences, we began to realize that perhaps we could generate a personalized cancer vaccine: that from the mutation profile of any patient, we could design peptides that encompass those mutations that were predicted to be immunogenic. We then devised a manufacturing strategy to combine up to 20 of those peptides into a vaccine that we could administer to patients as a series of skin injections over the course of several weeks.

I'm sure readers have heard and read a lot about cancer immunotherapy. How are vaccines related?

There are many different types of immunotherapy, and this fact reflects the many, many different functions and roles that T cells and other immune cells can play. Each immunotherapeutic modality leverages a different subset of those functionalities: A CAR-T cell or an immune checkpoint blockade are different from what a vaccine might do.

What they have in common, however, is that they are each stimulating immunity. A vaccine is trying to either generate new immune responses in an antigen-specific way that didn't exist before or amplify small pre-existing responses to become bigger. So, a vaccine has the potential to cast a wide immunoprotective "net" that can endure over time.

In your first study that came out in *Nature* in 2017, you treated six melanoma patients. Do we know how they're doing today?

I do know that three to four years after receiving the vaccine, all patients were still alive. We reported this result in 2021. Remarkably, two study patients who had very advanced cancer—stage IV disease—saw their cancer recur soon after vaccination. However, they both also got the immune checkpoint blockade, and within 12 weeks all detectable tumor

melted away.

It's been now about six or seven years since then and these patients are off therapy and doing really well. That's a huge success story and speaks to the strong positive synergy between vaccines and immune checkpoint blockade therapy.

What other types of cancer have been treated with these vaccines?

At Dana-Farber, we have treated patients in ongoing trials who have glioblastoma, kidney cancer, ovarian cancer, melanoma, and chronic lymphocytic leukemia. Separately, I also co-founded a company called Neon Therapeutics several years ago that conducted a larger study that treated patients with melanoma, lung, and bladder cancer.

Are these cancers chosen for any particular reason?

Cancer vaccines are cross-cutting as a treatment modality and can be tested in virtually any setting and in any cancer. Our selection has to do with the research questions that we are pursuing.

Are these all small, like the initial melanoma trial?

Yes. At Dana-Farber, our academic trials continue to be small phase 1 studies of 10 to 30 patients. Our focus has been to take deep dives into the study of every single patient to understand what our interventions are doing immunologically.

What's exciting is that now there is also a series of industry-sponsored studies—my research group is not involved in them—that are ongoing nationwide, even worldwide, that, hopefully within the next two or three

years, will give us a population-level view of the impact of such personal cancer vaccines. Last fall, the first randomized, phase 2 trial was reported out that demonstrated in melanoma the benefits of immune checkpoint blockade with a personalized cancer vaccine compared to immune checkpoint alone.

I think we're at an inflection point where the conceptual advantage of targeting many, many personal neoantigens simultaneously is undergoing rigorous testing. Such a personalized, multitarget approach is of conceptual importance because of the tremendous heterogeneity of tumor cell populations.

Even within one person's body?

Yes, exactly. And that is why a multipronged attack against cancer is favorable.

How big a hurdle is the fact that because these are so personalized, you have to find new neoantigens for each person in the trial?

It has its challenges. But with teams like ours at Dana-Farber—we are a collection of immunologists, clinical investigators, computational biologists, surgeons, and medical oncologists—we are able to design these vaccines together in real time. It certainly takes a village, and I am so grateful to be part of that village.

Given the challenge of coordinating the many parts of vaccine manufacture, this is an instance where partnering with industry is helpful, because they have the resources to develop processes at scale, streamlining costs, time, and labor. All of this is actively being figured out.

How far away are these vaccines from getting into the clinic?

Sooner than we think, because of academic innovations and industry-level efforts. Many large trials are ongoing now and I do think that they'll read out within two years. So, I hope that sometime in the not-too-distant future our patients can go to a clinic and say, "Order me up a vaccine personalized for my cancer," and we'll be able to administer it on-site.

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