UC San Diego Moores administers its first personalized cancer vaccine

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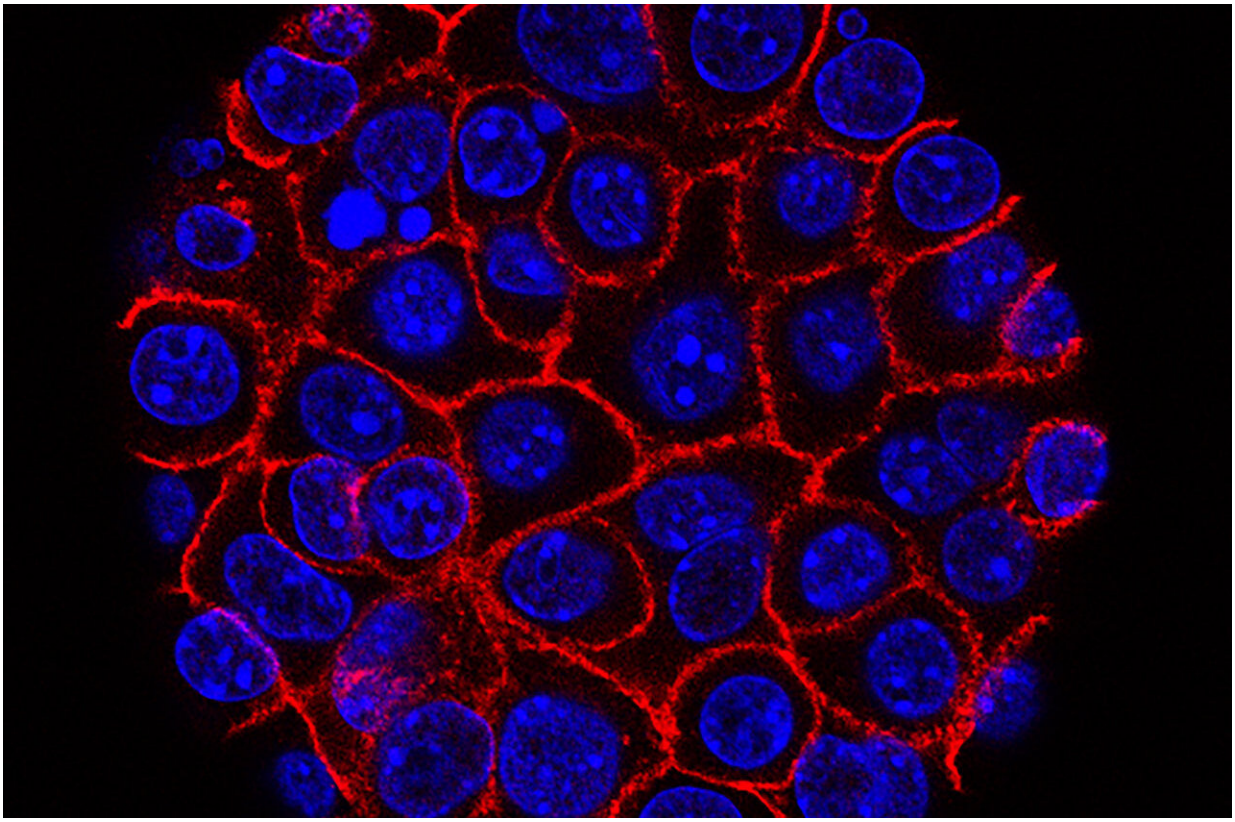

Credit: Min Yu (Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC),USC Norris Comprehensive Cancer Center

More than 18 rounds of chemotherapy and three abdominal surgeries have failed to slow the tumor that doctors discovered after Tamara

Strauss felt a suspicious lump in 2015.

Strauss was the first of 10 clinical trial patients to receive a personalized vaccine with the potential to do in just a few months what conventional treatments have failed to accomplish in three grueling years.

Unlike the scorched earth approach of chemo, cancer vaccines are exquisitely refined, containing immune system-activating molecules custom-made for each patient based on the specific genetic mutations present in their cancer cells.

Accepting patients with solid tumors of all types, the trial represents a significant new hope for the 59-year-old jewelry artist whose advanced cancer is rare and difficult to treat. But doctors hope to see progress, either halting the tumor's growth or reducing its size, in three to six months.

The effort is a collaboration of UC San Diego Moores Cancer Center and the La Jolla Institute of Allergy and Immunology and employs a basic approach just starting to show promise in small trials at other top-flight cancer centers worldwide.

But the local effort has its own special tweak that the San Diego researchers involved think will deliver greater precision in targeting the unique features of each patient's cancer cells.

The approach builds on basic research from the labs of immunologists Stephen Schoenberger and Bjoern Peters at the allergy institute and was brought to the bedside under collaboration with Dr. Ezra Cohen, director of translational science at Moores.

"The current method that everybody's using, it's highly-educated guessing but guessing all the same," Schoenberger said. "Our process

does take longer on the front end, but that's because we're taking the time to verify, rather than guess. We think it's going to make a big difference in our ability to be exactly on target."

Before slowly pressing the plunger forward, sending the first custom-crafted dose into Strauss's upper arm on Oct. 4, Cohen made it clear that the four years of collaboration necessary to arrive at that gives him confidence that the trial has a significant chance of success.

"I think this is a moment where history is happening, and we know it's happening," Cohen said.

The trial is made possible through a $1 million donation from well-known philanthropists and art collectors Matthew and Iris Strauss, who are Tamara Strauss's parents.

It is among a growing number of trials nationwide that capitalize on recent advances in genetic sequencing, bioinformatic analysis and manufacturing to craft vaccines loaded with molecules made to activate each patient's immune system against their tumor's specific genetic fingerprint.

Outside experts seem to agree that the approach moving forward at Moores in La Jolla is novel.

Microbiologist Fred Ramsdell, vice president of research at the Parker Institute for Cancer Immunology, a collaboration of high-flying cancer programs such as Harvard's Memorial Sloan Kettering Cancer Center, Stanford University, UCLA and MD Anderson Cancer Center, said the screening idea that the team in San Diego is putting into practice takes the cancer vaccine target selection process to a deeper level.

"One of the big things that Ezra and Stephen are doing is taking an

approach where they actually look for T-cell responses in the lab before making a vaccine," Ramsdell said. "Most everybody else makes their vaccines based on computational prediction alone."

Hard target

To date, other research efforts have taken samples of patients' tumors and healthy tissue, sequenced their genetic code, then compared the results, allowing scientists to spot mutations present in the cancer but not in healthy tissue. Those differences are used to predict changes in cancer antigens, the long chains of amino acids used by the immune system to tell the body's own cells from those of foreign invaders.

But it's not enough to simply predict which new antigens, or "neoantigens" as scientists call them, will likely be present.

T-Cells don't just encounter neoantigens and immediately get to work hunting down the cancer cells they match. Helper cells that are also part of the immune system, Schoenberger explained, must "present" the neoantigens to unprogrammed T-Cells in a very specific way using a class of molecules called major histocompatability complex or MHC.

This complicated dance involves MHC binding with neoantigens for presentation, and immunologists have learned through decades of research that MHC can vary from person to person.

So, in order to design an effective cancer vaccine, researchers must predict not only which neoantigens are most likely to be present in each candidate's cancer, but also which of those possible targets are likely to properly bind for presentation.

The new Moores trial attempts to do better by removing much of the guesswork from the target selection process.

In recent years, it has become clear that the immune system's normal surveillance process usually identifies at least a few neoantigens present in a patient's cancer even if the detection does not result in the surge of specifically-programmed T-cells necessary to win the fight.

Working together, Moores and the allergy institute have created a process where all predicted neoantigens can be manufactured and exposed to patient blood samples. Within two weeks, the process is able to flag antigens that are recognized by at least some of the T-cells present in the blood.

In Tamara Strauss's case, this blood culturing process allowed doctors to determine that three of the 27 neoantigens that computer models predicted have already been recognized by her immune system. Two of the three were used to make her vaccine. The third could not be included due to production difficulties.

The result, Schoenberger said, appears to be a 10-fold greater accuracy increase.

"From what we can tell, the algorithmic model is getting a hit rate of about 3 percent, but our functional approach is delivering about 35 percent, and we think that will make a big difference in effectiveness," Schoenberger said.

To help cope with a lower potential hit rate, other neoantigen trials tend to select up to 20 different targets for each vaccine. But that means that the immune system is likely to amplify many ineffective signals. The thought, Cohen explained, is that being able to confidently choose fewer targets for the immune system to pursue can significantly increase the effectiveness of the anti-tumor response.

"Our evidence in preclinical models would strongly suggest that picking

the right neoantigens is critical. In fact, if we load irrelevant antigens or ones that are not strongly reactive, we diminish the effect of the vaccine. More is not necessarily better. Getting it right is better," Cohen said in an email.

Long fight

Prone to hugging everyone she has come to know during her long span of treatment at Moores, Strauss has embraced both traditional and holistic methods to defeat her rare cancer, trying healing gems, focused meditation and many other alternative methods during her journey.

That duality was present on Oct. 4 as Lanie Chapman, Strauss's friend and a Reiki healing touch master, bestowed an energy blessing on the syringe containing her vaccine before it was administered. Strauss said she has had no trouble pursuing traditional and holistic methods simultaneously.

"They're meant to work together," Strauss said. "The chemotherapy, this vaccine, they're what can save my life, but the holistic, I think that's what has helped offset a lot of the damage that the cancer and the medicine have done to my body."

The Strauss family has suffered more than its fair share of cancer pain.

Iris and Matthew Strauss lost their daughter, Stefanie, to ovarian cancer in 2010. That experience prompted the Rancho Santa Fe couple, which has had significant success in real estate, to fund a center that is building a new genetic test for early ovarian cancer detection.

Shortly after Tamara's diagnosis in 2015, a dinner with the late Ralph Whitworth, the well-known activist investor who died of cancer complications in 2016, turned the couple on to the neoantigen work

underway at the allergy institute.

When it became clear that the only way to extend these ideas to his daughter was to fund a clinical trial, Matthew Strauss wrote a check, but not before diving into the evidence. He worked to expand his microbiological fluency, filling his cellphone with page after page of terms, a custom mobile glossary he could refer to time and time again as he traveled to scientific conferences and familiarized himself with the intricacies of cancer immunotherapy.

"We made this decision based on knowledge, not just emotion. When they came up with a full written treatment protocol, it seemed clear that this is a rare chance not just to help Tammy, but for the greater good," Matthew Strauss said during an interview at Moores in late 2017.

While they do agree that the Moores approach is novel, experts also note that nothing here on the edge of cancer knowledge is for sure.

No guarantees

Ramsdell, the Parker Institute microbiologist, explained that there is no guarantee that more accurate T-cell targeting will produce the kind of vigorous anti-tumor attack that oncologists and patients desire. The immune system is vastly complex and not yet fully understood.

"If the patient's immune system does respond to the neoantigens they select, you don't know how efficient or effective those T-cells that get activated are going to be," he said. "It is possible that the patient makes a response, but that response doesn't have the right effect."

And killing stubborn tumors is about more than proper targeting, adds Dr. Siwen Hu-Lieskovan, a clinical oncologist at David Geffen School of Medicine at UCLA. The clinician and researcher is UCLA's lead

investigator for an ongoing neoantigen trial by Boston-based Neon Therapeutics.

Cancer cells, she noted, create significant changes in their immediate surroundings, what scientists call their microenvironment. Those changes serve to inhibit the effectiveness of the immune system's attack forces, including the types of T-cells that the trial seeks to multiply and mobilize.

"How to effectively address the tumor microenvironment is one of the biggest challenges we have in immunotherapy research at the moment," Hu-Lieskovan said.

She also questioned the 12-week lead time specified for vaccine screening and manufacture in the Moores study design. Current trials that just use computer prediction, rather than functional blood-based screening, are significantly shorter and, often, patients with late-stage cancer don't have long to wait.

"It's hard for me to imagine that many patients can wait that long," Hu-Lieskovan said.

Standing in the hallway outside Strauss's infusion room, Schoenberger said that 12-week timeframe is actually weeks longer than it has actually taken to produce a custom vaccine as was selected as the maximum-possible wait.

Plans are underway, he added, to significantly shorten the six- to eight-week vaccine manufacturing process, which currently occurs at a facility in Europe.

And, the entire blood culture process, the researcher added, may not be necessary for long. As research in the allergy institute's wet lab builds a

list of which neoantigens bind with which MHC molecules, that information can be used to better train neoantigen prediction algorithms.

As to handling the tumor microenvironment, he said each patient will receive immunotherapy pembrolizumab, a drug commonly marketed as Keytruda, to push back against these effects. Among a new class of "checkpoint inhibitors," Keytruda blocks a cellular off switch on T-cells that many types of cancer can activate to evade eradication.

"Using Keytruda with the vaccine tackles one of the major inhibitory effects of the cancer microenvironment, and we've used exactly this strategy in preclinical models. In mice where the microenvironment is certainly present, we've cured considerable tumors," Schoenberger said.

Patients in the new trial at Moores will receive three vaccine doses, one every three weeks. Cohen said researchers will take a first look at the state of Strauss's pancreatic neuroendocrine cancer about 9 weeks after the first dose. Unlike pancreatic adenocarcinoma, which often has a prognosis of only a few months, the subtype that Strauss is fighting is significantly less aggressive.

Initially, Cohen noted, researchers will look for evidence that trial participants' immune systems have received and responded to the neoantigenic message that the vaccine has delivered. Shrinking or even eliminating tumors could take many additional months.

Sitting on a bed at Moores in a red velvet dress with her mother holding her hand, Strauss had her own thoughts about messages received. She noted that the date she got her shot was Oct. 4 which is abbreviated 10-4. Those numbers, she mused, do have a very specific meaning in communications.

"It means, 'yes, got your message.' That's kind of profound. Maybe the

universe has gotten the message?" Strauss said.