Improving Cancer Vaccines With T-Cell Programming Nanoparticles

Matthias Stephan, MD, PhD, receives grant to develop cancer vaccine–optimizing, TCR-programming nanotechnology.

August 20, 2018 By Sabrina Richards

Fred Hutchinson Cancer Research Center immunobioengineer Matthias Stephan, MD, PhD, has received a 2018 Investigator's Award in Cell and Gene Therapy for Cancer from the Alliance for Cancer Gene Therapy to support the development of a combined T-cell programming, cancer-vaccine strategy to treat cancer. His proposed method, which unites nanoparticles that carry cancer vaccine–specific T-cell receptor genes with a vaccine designed to trigger an immune response to a patient's tumor, aims to improve the effectiveness of therapeutic cancer vaccines by guaranteeing that the patient has cancer-specific T cells capable of responding to the vaccine.

"We're making sure that there's a small population of vaccine-specific, T-cell receptor–engineered T cells [to respond to the vaccine]," Stephan said. He will receive $500,000 over three years to support the project.

Filling an immune hole

Therapeutic cancer vaccines — those designed to encourage the body to attack a tumor that's already growing — hold much promise. In theory, the body can be stimulated to recruit its own cancer-specific immune cells, known as T cells, to hunt down cancer cells. But in practice, only one therapeutic cancer vaccine, sipuleucel-T, has ever been approved by the Food and Drug Administration.

The main hurdle is that no matter how well-designed a cancer vaccine may be, it can't work unless tumor-specific T cells are already present in the patient, Stephan said. But often, through bad luck or age-related declining immune function, these cells may not be part of an individual's immune repertoire. Alternatively, cancer-specific immune cells that do exist are often low- affinity cells that won't mount the powerful response needed to shrink a tumor.

Stephan's solution is to deliver the key T-cell specificity with the vaccine itself. The strategy builds on previous work in which he showed that he could use nanoparticles to carry cancer-targeting, genetic reprogramming instructions to T cells still inside mice in a preclinical model of leukemia. Now, Stephan and postdoctoral fellow Fan Zhang, PhD, are joining these nanoparticles with a

cancer vaccine in a single intramuscular injection.

The tumor-specific protein they've chosen to target initially is mesothelin, a protein highly expressed in pancreatic and ovarian tumors but only negligibly in healthy tissue. In this approach, the researchers will provide a new T-cell receptor, or TCR, the molecule that T cells use to recognize target cells. The TCR genes Zhang and Stephan will package into nanoparticles encode an anti-mesothelin TCR developed by Hutch colleagues that is already moving into clinical trials of pancreatic cancer patients.

If the approach works, it should work for all, Stephan said. "The idea is that none of the patients should fail because all patients will have anti-cancer T cells. We have complete control over T-cells' specificity," he explained. "We can immunize irrespective of immune status; if they're immunocompromised, if they had chemotherapy, are old or young — as long as they have some T cells."

The proposed approach is also flexible. Zhang and Stephan have plans to target two types of T cells using separate strategies: T cells that can directly kill cancer and helper T cells that rally an anti-cancer immune response. Cancer cell–killing T cells can be permanently programmed to carry cancer-specific TCR genes that will make it possible for them to seek out and destroy tumor cells for the rest of their lives. Helper T cells, in contrast, could be temporarily programmed with cancer recognition to help jumpstart a broader immune response to the tumor.

Beyond cancer

Though Stephan's initial studies focus on cancer, his strategy potentially could help improve efficacy for vaccines against infectious diseases as well. Certain other vaccines, such as the hepatitis B vaccine, don't strongly stimulate the immune system. In the case of the flu vaccine, many of those who would most benefit from it — the elderly — don't have the robust immune systems needed mount a strong and lasting response. Providing immune specificity with the vaccine could help build protections in certain patient populations or for less-immunostimulatory vaccines.

But for now, Stephan and Zhang are focusing on cancer. They will test their strategies in preclinical models of pancreatic ductal adenocarcinoma and ovarian cancer. The award's indirect costs are covered by the Hutch's Reservoir Fund, which provides support for faculty members who have received awards from foundations that do not cover the full indirect cost rate.

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