Vaccines may make war on cancer personal

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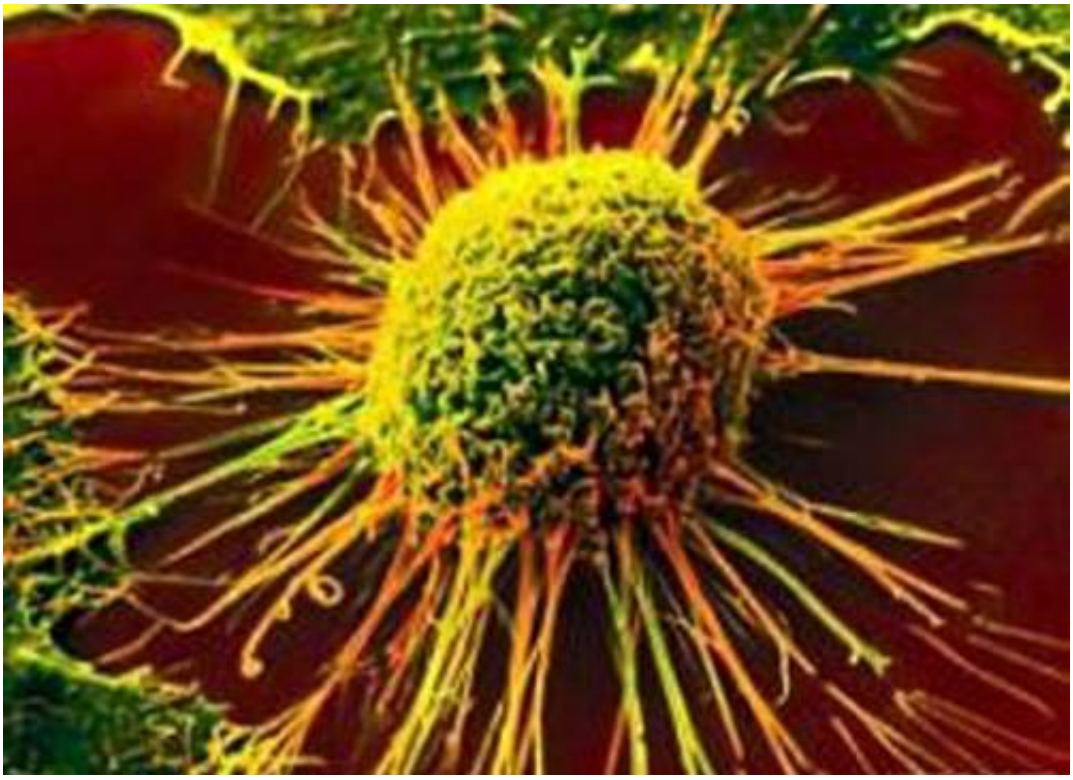

In the near future, physicians may treat some cancer patients with personalized vaccines that spur their immune systems to attack malignant tumors. New research led by scientists at Washington University School of Medicine in St. Louis has brought the approach one step closer to reality.

Like flu vaccines, cancer vaccines in development are designed to alert

the immune system to be on the lookout for dangerous invaders. But instead of preparing the immune system for potential pathogen attacks, the vaccines will help key immune cells recognize the unique features of cancer cells already present in the body.

Scientists at Washington University already are evaluating personalized cancer vaccines in patients with metastatic melanoma in a clinical trial led by Gerald Linette, MD, PhD, and Beatriz Carreno, PhD at Siteman Cancer Center. The researchers also are working to use the vaccines against breast, brain, lung, and head and neck cancers, and additional trials are anticipated in the next year or two.

In the new study, which appears Nov. 27 in an issue of *Nature* focused on cancer and the immune system, scientists tested investigational vaccines in computer simulations, cell cultures and animal models. The results showed that the vaccines could enable the immune system to destroy or drive into remission a significant number of tumors. For example, the vaccines cured nearly 90 percent of mice with an advanced form of muscle cancer.

"This is proof that personalized cancer vaccines can be very powerful and need to be applied to human cancers now," said senior author Robert Schreiber, PhD, the Alumni Professor of Pathology and Immunology and director of the university's Center for Human Immunology and Immunotherapy Programs.

Creating a personalized vaccine begins with samples of DNA from a patient's tumor and normal tissue. Researchers sequence the DNA to identify mutant cancer genes that make versions of proteins found only in the tumor cells. Then they analyze those proteins to determine which are most likely to be recognized and attacked by T cells. Portions of these proteins are incorporated into a vaccine to be given to a patient.

Years of studying cancer genetics and of the immune system's interactions with cancer have made the vaccine strategy possible.

The technique was inspired by a therapy scientists call checkpoint blockade. This immune-based cancer treatment, which has been successful against advanced lung and skin cancers in clinical trials, takes advantage of immune T cells that are present in many tumors but have been shut off by cancer cells.

The cancer cells shut off the T cells by activating a safety mechanism called the checkpoint system. This system helps prevent immune cells from attacking the body's own tissues.

Checkpoint blockade takes the brakes off T cells, unleashing their destructive capabilities on the tumors. But the approach also increases the chances that those same immune cells erroneously will attack healthy tissue, causing serious autoimmune disease.

"We thought it would be safer to find ways to identify the mutated tumor proteins that are the specific targets of the reactivated T cells that attack the tumors," Schreiber said. "We believe we can incorporate those proteins into vaccines that only unleash the T cells on the tumors, and so far, our tests have been very successful."

More information: Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, Ivanova Y, Hundal J, Arther CD, Krebber W-J, Mulder GE, Toebes M, Vesely MD, Lam SSK, Korman AJ, Allison JP, Freeman GJ, Sharpe AH, Pearce EL, Schumacher TN, Aebersold R, Rammensee H-G, Melief CJM, Mardis ER, Gillanders WE, Artyomov MN, Schreiber RD. Checkpoint blockade cancer immunotherapy targets tumor-specific mutant antigens. *Nature*. Nov. 27, 2014. DOI: 10.1038/nature13988

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