

Using the body's own immune system in the fight against cancer

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DNA sequences from tumor cells can be used to direct the immune system to attack cancer, according to scientists at Washington University School of Medicine in St. Louis.

The research, in mice, appears online Feb. 8 in *Nature*.

The [immune system](#) relies on an intricate network of alarm bells, targets and safety brakes to determine when and what to attack. The new results suggest that scientists may now be able to combine DNA sequencing data with their knowledge of the triggers and targets that set off immune alarms to more precisely develop vaccines and other immunotherapies for cancer.

"We already have ways to identify specific targets for immunotherapy, but they are technically challenging, extremely labor-intensive and often take more than a year to complete," says senior author Robert Schreiber, PhD, the Alumni Professor of Pathology and Immunology at the School of Medicine and co-leader of the tumor immunology program at the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. "These difficulties have stood in the way of developing personalized immunotherapies for [cancer patients](#), who often require immediate care for their disease. To our knowledge, this is one of the first studies to show that the faster methods provided by DNA sequencing can help. That opens up all kinds of exciting possibilities."

Scientists have long maintained that the immune system can recognize cancer as a threat either on its own or with the help of vaccines or other immunotherapeutic treatments, which help alert the immune system to the danger posed by cancers. Once the cancer is recognized, the immune system should develop the capacity to attack growing cancer cells until either the tumor is eradicated or the immune system's resources are

exhausted.

Schreiber and his colleagues have shown that interactions between the immune system and cancer are more complex. Their theory, called cancer immunoediting, suggests that some of the [mutations in tumor cells](#) are very easy for the immune system to recognize as a threat. If the immune system detects these mutations in cancer cells, it attacks until they are destroyed.

At that point, the cancer may be eliminated. But it's also possible that the cancer can be "edited" by the immune system, resulting in the removal of all the cells containing the critical easily recognized mutations. The remaining tumor cells can continue to grow or enter into a period of dormancy where they are not destroyed but are held in check by the immune system.

For the new study, Schreiber and his colleagues wanted to define the genetics of tumors that had yet to interact with the immune system. To do so, they induced tumors in mice with disabled immune systems. They collaborated with Washington University's Genome Institute scientists, who sequenced the cancer cells' genes.

"Until very recently, this work would have been impractical because of the costs involved," Schreiber says. "But the technology has improved and prices have come down, and now it's possible to obtain this genetic information for a few thousand dollars instead of a million."

By comparing genetic data from cancer cells and normal cells, scientists identified 3,743 mutations in the genes of the tumor cells. Next, they turned to an online database of protein sequences likely to be recognized by a key immune system sensor. This helped them narrow their focus to a few mutated genes whose altered proteins seemed most likely to trigger immune system attacks. One of these mutated proteins, an altered form of

spectrin-beta2, was present in all tumor cells that were attacked by the immune system and in none of the cells that were ignored.

Researchers cloned this mutant gene and put it into other mouse tumor cells that lacked the mutation. When transplanted into mice with normal immunity, the tumor cells that made the mutant spectrin-beta 2 protein were attacked and eliminated by immune cells.

"Many of the cancer genome projects now under way are looking for the 'driver' mutations, or the mutations that cause the cancers," Schreiber says. "Our results suggest there may be additional information in the sequencing data that can help us make the immune system attack cancers."

Schreiber calls the spectrin-beta2 mutation identified in the study "low-hanging fruit," noting that it's such a red flag to the immune system that its presence normally leads the immune system to assault [cancer cells](#) without any prompting from [immunotherapy](#).

He and his colleagues are currently sequencing DNA in tumors grown from mice with normal immune systems to see if they can identify mutations that are not as readily discernible to the immune system.

"The idea would be to make a [vaccine](#) that helps the immune system recognize and attack six or seven of these mutated proteins in a cancer," he says. "Therapeutically, that could be very helpful."

More information: Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, Arthur CD, White JM, Chen Y-S, Sheak LK, Hundal J, Wendl MC, Demeter R, Wylie T, Allison JP, Smyth MJ, Old LJ, Mardis ER, Schreiber RD. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. *Nature*, online Feb. 8, 2012.

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