

New approach identifies cancer mutations as targets of effective melanoma immunotherapy

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A new approach demonstrated that the recognition of unique cancer mutations appeared to be responsible for complete cancer regressions in two metastatic melanoma patients treated with a type of immunotherapy called adoptive T-cell therapy. This new approach may help develop more effective cancer immunotherapies, according to a study published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

"This study provides the technical solution to identify mutated tumor targets that can stimulate immune responses, which is one of the major bottlenecks in developing a new generation of adoptive T-cell therapy," said Steven A. Rosenberg, MD, PhD, chief of surgery at the National Cancer Institute (NCI) in Bethesda, Maryland. "The two targets identified in this study play important roles in cancer cell proliferation.

"Immunotherapy has the potential to successfully treat cancer by targeting tumor mutations. We've moved one step closer because of this study," Rosenberg added.

Adoptive T-cell therapy is a type of [immunotherapy](#) in which the immune cells infiltrating a patient's tumor, so called tumor-infiltrating lymphocytes (TILs, which are T cells), are harvested, activated and expanded in the laboratory, and transferred back to the patient. Such activated cells are capable of efficiently attacking [tumor cells](#).

"In a clinical trial, up to 72 percent of the patients with [metastatic melanoma](#) experienced tumor regression after adoptive T-cell transfer. However, not all patients benefited. This is because the specificity of the TILs remains largely unclear. Our goal was to establish an efficient method to identify the specificity of these cells," explained

Rosenberg.

The researchers took tumor samples from two patients who had benefited from the therapy and pursued two screening approaches to identify the tumor targets recognized by the clinically effective T cells. First, they used a conventional screening method called cDNA library screening to identify nonmutated targets. Second, they used a novel method called tandem minigene library screening to identify mutated targets that cannot be found by the conventional method of screening.

For the second approach, the researchers used next-generation DNA sequencing to sequence the coding regions of the DNA from the two patients' tumors, and identified mutations. Next, they generated a library of these mutations. Instead of synthesizing the entire mutated gene, they synthesized only a small region surrounding the mutation (hence the name "minigene" library). They then screened the minigene library to identify those targets in the [patients'](#) tumors that were recognized by their TILs.

Using cDNA library screening, the researchers identified three novel nonmutated tumor targets, and four previously known non-mutated tumor targets.

Using tandem minigene library screening, they identified two novel mutated tumor targets, KIF2C and POLA2, which play important roles in cell proliferation.

With the minigene library approach, Rosenberg and colleagues recently reported another novel [tumor](#) target recognized by the activated T cells of a patient with bile duct [cancer](#), who responded to adoptive T-cell transfer.

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