

RNA “Typos” Can Highlight Leukemia Cells for Immune Attack

Looking beyond DNA, scientists find possible “surgically targeted” option for splicing factor-mutant blood cancers that lack effective immunotherapies.

May 5, 2025 By Fred Hutch News Service and Sabrina Richards

Cancers driven by hiccups in RNA processing can’t hide from our immune system, according to [new work](#) published April 23 in *Cell*. A cross-institutional team Fred Hutch Cancer Center and Memorial Sloan Kettering Cancer Center (MSK) found that common splicing factor mutations in myelodysplastic syndrome or acute myeloid leukemia cells create tell-tale, cancer-specific molecular “typos” that sharp-eyed immune cells can read.

The collaborators also isolated, for the first time, immune cells that can recognize and kill leukemia cells with these genetic misspellings while leaving healthy cells unharmed.

The Fred Hutch and MSK scientists hope their findings lay the foundation for an off-the-shelf cellular immunotherapy for patients with MDS or AML driven by these splicing factor mutations.

“We’re able to find natural features of the cancer themselves that are targetable,” said Fred Hutch RNA splicing expert and co-senior author [Robert Bradley, PhD](#), who holds the McIlwain Family Endowed Chair in Data Science. “It’s exciting because it’s a new way of thinking about how the immune system can recognize cancers: It doesn’t have to just come from lots of mutations in the tumor.”

The immune cells (called T cells) that the team identified “could [form] a new class of immunotherapy that could be applicable to up to 70% of patients with MDS and a large percentage with AML,” said MSK oncologist, leukemia researcher and co-senior author [Omar Abdel-Wahab, MD](#).

The approach, if successful, will lead to a [cellular immunotherapy](#) that’s more tailored than current CAR T cells (the most common FDA-approved type of cellular cancer immunotherapy).

“In many ways, I think this is the beginning of the clinical development of an entirely new class of therapy,” said MSK immunotherapy researcher and co-senior author [Christopher Klebanoff, MD](#). “Currently there’s not an approved TCR [T-cell receptor] therapy specifically for liquid tumors, which is a gap that hopefully one day we’ll be able to fill based on results from this new study.”

T cells decipher molecular misprints

T cells are our bodies' security guards: they keep the peace and eject the riffraff. To keep us healthy, T cells use highly specialized molecules called T-cell receptors, or TCRs, to detect changes in the spectrum of proteins a cell makes. Often this is due to a viral infection, but DNA mutations or misspellings that drive cancer can also lead to changes in amino acid sequences.

And like bouncers with an eye for fake IDs, T cells can spot (and eliminate) these protein "misprints."

Sometimes a protein's amino acids can change even if its gene remains normal.

This can happen due to changes in RNA splicing, the highly regulated process of properly editing RNA molecules before they get read by our cells' protein-building factories.

Problems in RNA splicing can lead to "typos" that get reproduced in a protein's amino acid sequence. Sometimes these new proteins can push biological processes like growth and division into high gear. In fact, mutations that reduce splicing factors' copyediting ability can result in wide-ranging protein misprints that drive certain leukemias and leukemia-like syndromes such as MDS.

Bradley and Abdel-Wahab have a long-standing collaboration working out how mutations in certain splicing factor genes drive leukemia, with an eye toward leveraging the knowledge to develop new treatments.

"We were wondering, could cancers with mutations in the splicing machineries just on their own generate novel proteins that could be really amazing therapeutic targets — if we could figure out what those novel proteins are and what the immune cells that recognize them are," Abdel-Wahab said.

His and Bradley's work had already hinted that the answer was yes: In a previous study, they showed that forcing leukemia cells to generate more RNA typos and protein misprints can make those cells [more visible to the immune system](#).

But current T-cell based cancer immunotherapies don't work effectively for all types of leukemia and are not yet an option for some neoplasms, like MDS. The only FDA-approved cellular therapy using a TCR instead of CAR treats [metastatic synovial sarcoma](#), a rare connective tissue cancer.

They had two goals: Identify tell-tale protein misprints (or "neoantigens") found across blood cancers with splicing factor mutations, and find T cells that can recognize them.

To Bradley's RNA splicing know-how and Abdel-Wahab's clinical experience, the team added Klebanoff's expertise in TCR-based immunotherapy.

Splicing factor mutations produce neoantigens

In many cases of MDS and AML, altered RNA splicing patterns are clearly linked to mutations in specific genes. The team suspected that shared splicing factor mutations would be reflected in shared patterns of splicing-related neoantigens.

Abdel-Wahab's group had collected tissue samples from patients with MDS and AML. Bradley's team used these samples to compare RNA splicing patterns between blood cancer cells carrying mutations in the splicing factor genes SF3B1, SRSF2, U2AF1, or ZRSRZ2 and healthy, unmutated bone marrow cells. They found that cancer cells from many patients shared the same mis-splicings not seen in normal bone marrow.

The team then used an artificial neural network algorithm to predict which typo-riddled proteins would be most likely to be spotted by T cells.

T cells that detect mis-splicings can kill leukemia cells

When T cells run their inspections, they read bits of proteins displayed on molecular signposts called HLA molecules (for human leukocyte antigen), or MHC (for major histocompatibility complex).

"These HLA molecules allow T cells to see inside other cells, a process akin to giving immune cells X-ray vision," Klebanoff said. The bits of proteins (called peptides) hung on HLA pegs come from proteins found everywhere in the cell. CAR T cells, the most common type of cellular cancer immunotherapy, only detect proteins located on a cells' surface.

The neoantigens most likely to draw T-cell attention are those whose peptides best fit into HLA proteins. HLA genes vary widely among people, so the team looked for peptides that bind best to some of the most common HLA variants. In particular, they focused on a neoantigen formed by a mis-splicing in a protein called CLK3 that fits in HLA-A*02:01.

Using technology developed by Klebanoff's group, the researchers were able to isolate killer T cells from healthy donors that recognize and react to the CLK3 neoantigen displayed on HLA-A*02:01. The TCR genes from these cells conferred this same responsiveness to other T cells.

T cells bearing these TCRs successfully killed off AML cells with mutated SRSF2 with HLA-A*02:01, but not those with unmutated SRSF2 or a different HLA type. When they tested the TCRs in a preclinical model of AML, in which human tumor cells are grown in mice, they found that mice treated with T cells carrying the anti-CLK3 neoantigen TCRs had a lower tumor burden compared to mice treated with T cells that recognized a different target.

Abdel-Wahab estimated that he and Bradley had spent about 10 years "defining those mis-splicing events that are created reproducibly across patients, and now we just translated that to new antigens and TCRs with Chris' help."

Next steps

Much work remains before an immunotherapy based off this concept will reach patients, but the scientists are optimistic. Because the neoantigens they identified are shared among patients, TCRs against them “really lend themselves to an off-the-shelf therapy as opposed to something that is entirely individualized,” Klebanoff said.

Bypassing the need to hunt for a neoantigen (and TCR) unique to each patient, ready-made TCR-based cellular therapies would be faster, cheaper and easier to scale up, he said.

This class of targets “is shared in common to — and unique to — cancer cells, but represents a target that is not expressed by normal hematopoietic [bone marrow] stem cells or healthy tissue,” Klebanoff said. This would allow a T-cell therapy aimed at RNA splicing factor mutants to be “surgically targeted” with reduced risk of damage to healthy tissues.

To serve a wide array of leukemia patients, the collaborators are working to identify a panel of TCRs against a variety of neoantigens created by splicing defects in different HLA variants.

They also hope to extend the strategy to other cancers with RNA splicing defects. Many cancers, including difficult-to-treat types of pancreatic and breast cancer also exhibit RNA splicing aberrations, and these patients need new treatment options. But this will likely require more basic research into RNA splicing changes in solid tumors, Bradley said.

“We need to develop an understanding of splicing dysregulation across most cancers that parallels the excellent understanding we have in the case of splicing factor mutations in leukemia,” he said. “That would serve as a foundation both for our fundamental biological knowledge, but also for identifying specific neoantigens that are going to be the most productive for targeting across many patients.”

For now, the team is excited about the potential to exploit a cancer driver in order to better treat patients.

“Having these splicing factor mutations is not a good thing, but we’re able to turn it on its head,” Bradley said. “They can be exploited to create a precision immunotherapy.”

Federal Funding Helps Us Save Lives

At Fred Hutch, 70% of our research funding comes from federal grants, which are awarded based on scientific merit. This level of federal funding is a direct reflection of our proven ability to make landmark breakthroughs and our trusted ability to lead large scientific collaborations.

[Learn more](#)

This work was funded by the National Institutes of Health, the National Cancer Institute, Break Through Cancer Foundation, the Neil S. Hirsch Foundation, the American Society of Hematology, the Damon Runyon Cancer Research Foundation, the Edward P. Evans Foundation, the Metropoulos Family Foundation, the Parker Institute for Cancer Immunotherapy, the Blood Cancer Discoveries Grant program through The Leukemia & Lymphoma Society, The Mark Foundation for Cancer Research and The Paul G. Allen Frontiers Group.

Sabrina Richards, a senior editor and writer at Fred Hutch Cancer Center, has written about scientific research and the environment for The Scientist and OnEarth Magazine. She has a PhD in immunology from the University of Washington, an MA in journalism and an advanced certificate from the Science, Health and Environmental Reporting Program at New York University. Reach her at srichar2@fredhutch.org.

[This article](#) was originally published April 23, 2025, by Fred Hutch News Service. It is republished with permission.

© 2026 Smart + Strong All Rights Reserved.

<http://beta.docker.cancerhealth.com/article/rna-typing-can-highlight-leukemia-cells-immune-attack>