New biotechnology combines targeted and immune therapies to kill treatment-resistant cancer cells

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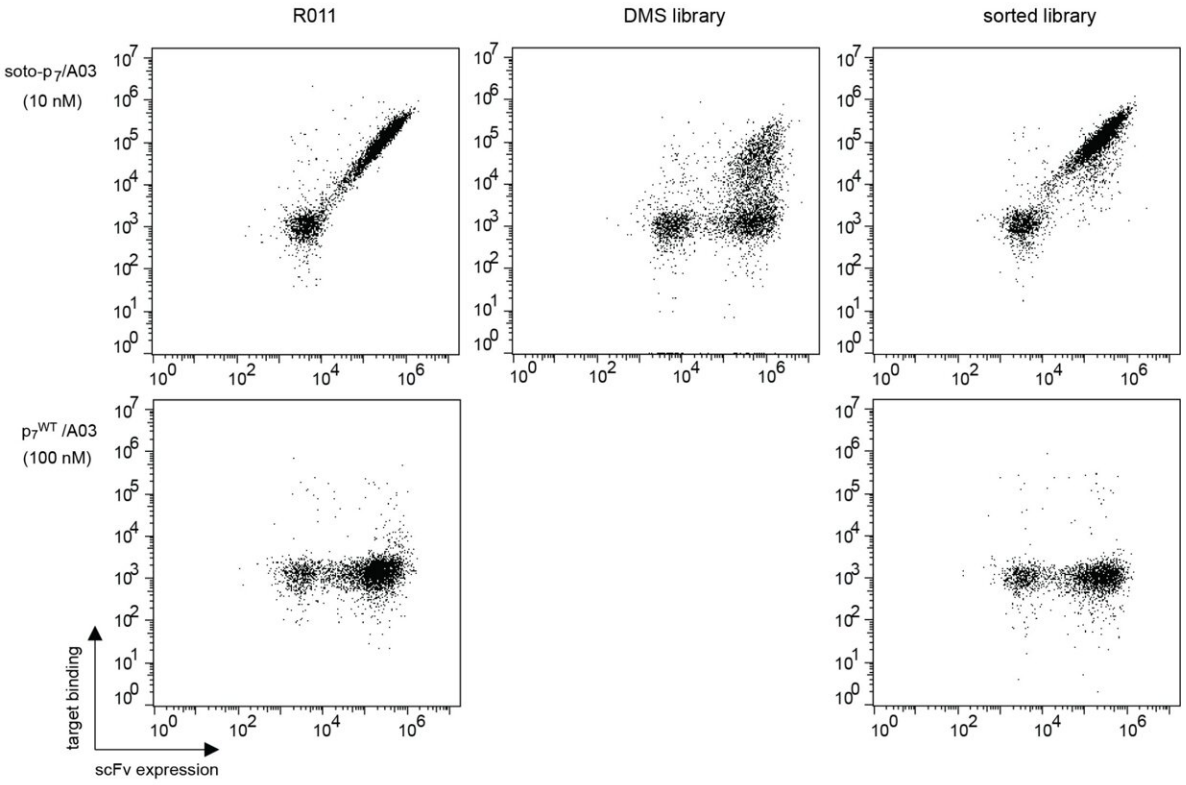

Binding profiles soto-p_7/A03 (top row) and p_7^{WT}/A03 (bottom row) of clone R011 (left column), the naïve deep mutational scanning library (middle column), and the pool after sorting for binding to soto-p_7/A03 (right column) tested in the yeast-display format. Credit: *Cancer Discovery* (2022). DOI: 10.1158/2159-8290.CD-22-1074/709728

Targeted therapies specifically attach to and hinder cancer-causing proteins, but cancer cells can quickly evolve to thwart their action. A second drug class, immunotherapies, harnesses the immune system to attack cancer cells, but these agents often cannot "see" the disease-causing changes happening inside cancer cells, which look normal from the outside.

Now, a new study led by researchers from the Perlmutter Cancer Center at NYU Langone Health describes a strategy to overcome these limitations based on several insights. First, the research team recognized that certain targeted drugs called "covalent inhibitors" form stable attachments with the disease-related proteins they target inside cancer cells. They also knew that proteins once inside cells are naturally broken down and presented as small pieces (peptides) on cell surfaces by major histocompatibility complex (MHC) molecules. Once bound to MHC, peptides are recognized as foreign by the immune "surveillance" system if they are sufficiently different from the body's naturally occurring proteins.

Although tumor cells usually develop ways to escape immune surveillance, the study authors reasoned that a cancer-related peptide target tightly bound to its covalent inhibitor could act as an MHC-displayed "flag" that could be recognized by immune proteins called antibodies. The team then engineered such antibodies and joined them to another antibody known to "recruit" T lymphocytes, the "killer cells" of the immune system, to form "bi-specific" antibodies that destroyed tumor cells.

"Even when genetic and other changes frustrate targeted therapies, they often still attach to their target proteins in cancer cells, and this attachment can be used to label those cells for immunotherapy attack," says co-corresponding study author Shohei Koide, Ph.D., professor in the Department of Biochemistry and Molecular Pharmacology and a

member of Perlmutter Cancer Center at NYU Langone. "Further, our system, conceptually, has the potential to increase the efficacy of any cancer drug when attached to the drug's disease-related target where the combination can be displayed by MHCs."

Published online October 17 in *Cancer Discovery*, the new study tested the researchers' approach on two FDA-approved, targeted drugs, sotorasib and osimertinib. Recently approved based on a study co-led by NYU Langone researchers, sotorasib works by attaching to an altered form of the protein KRAS called p.G12C, in which a glycine building block has been mistakenly replaced by a cysteine in its structure. This change causes the KRAS protein switch to become "stuck in the on mode" and signal for abnormal growth. Sotarasib effectively blocks this activated signal to start, but cancer cells rapidly become resistant.

In experiments with KRAS mutant cancer cells grown in a dish (cell cultures), the team's HapImmune antibodies recognized, recruited T cells, and led to the killing of treatment-resistant lung cancer cells, in which sotorasib attached to its target, KRAS p.G12C, and was displayed by MHCs. The team also developed bi-specific antibodies that bound to a peptide "flagged" with osimertinib, a drug that targets an altered form of epithelial growth factor receptor seen in other lung cancers, as well as prototypes that "saw" the drug ibrutinib when linked to its target, BTK, showing the technology's "broad potential," the researchers say.

Harnessing display

The study revolved around the process where proteins inside human cells are broken down and replaced as a part of the normal lifecycle. Alongside this turnover runs an inspection system, in which protein fragments are delivered to a cell's surface. T cells inspect these displayed complexes, and can notice, for instance, when a cell is displaying viral proteins, a sign that the cell is infected with a virus. The T cells then

direct the killing of the virally infected cells.

The immune system can in some cases also recognize cells with cancerous changes underway inside by the proteins they display on their surfaces. However, because cancer-driving proteins arise from normal proteins, with differences between cancerous and normal fragments often minute, the system struggles to tell them apart. Even when patients develop T cells that can see these small differences, tumors respond with mechanisms designed to "exhaust" anti-tumor cells. In seeking to counter these mechanisms, the team's central realization was that, among the proteins displayed by MHCs are fragments carrying drugs taken in by cells, which could be targeted by antibodies.

The current study also found that the team's platform was effective against KRAS p.G12C mutant cells with different MHC types, also called human leukocyte antigen (HLA) supertypes. Usually, there is a strict pairing between MHC/HLA types and antibodies built to interact with certain T cells, which could potentially restrict the number of patients that could treated by this approach. The new study showed that the team's antibodies recognize multiple MHC/HLA types, and so, in principle, could be deployed in 40–50 percent of the US patient population with tumors bearing KRAS p.G12C.

"Our results further show that the antibodies attach to drug molecules only when presented by MHCs on cells, and so could be used in combination with a drug," says study co-corresponding author Benjamin G. Neel, MD, Ph.D., director of NYU Langone Health's Perlmutter Cancer Center. "When used in combination with such antibodies, a given drug would only need to flag cancer cells, not fully inhibit them. This creates the possibility of using drugs at lower doses, potentially, for reducing the toxicity sometimes seen with covalent inhibitors."

Moving forward, the research team plans to study their platform in live

animal models, using more pairs of drugs and the disease-related protein fragments they target.

More information: Shohei Koide et al, Creating MHC-restricted neoantigens with covalent inhibitors that can be targeted by immune therapy, *Cancer Discovery* (2022). DOI: 10.1158/2159-8290.CD-22-1074/709728. aacrjournals.org/cancerdiscove … 90.CD-22-1074/709728

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