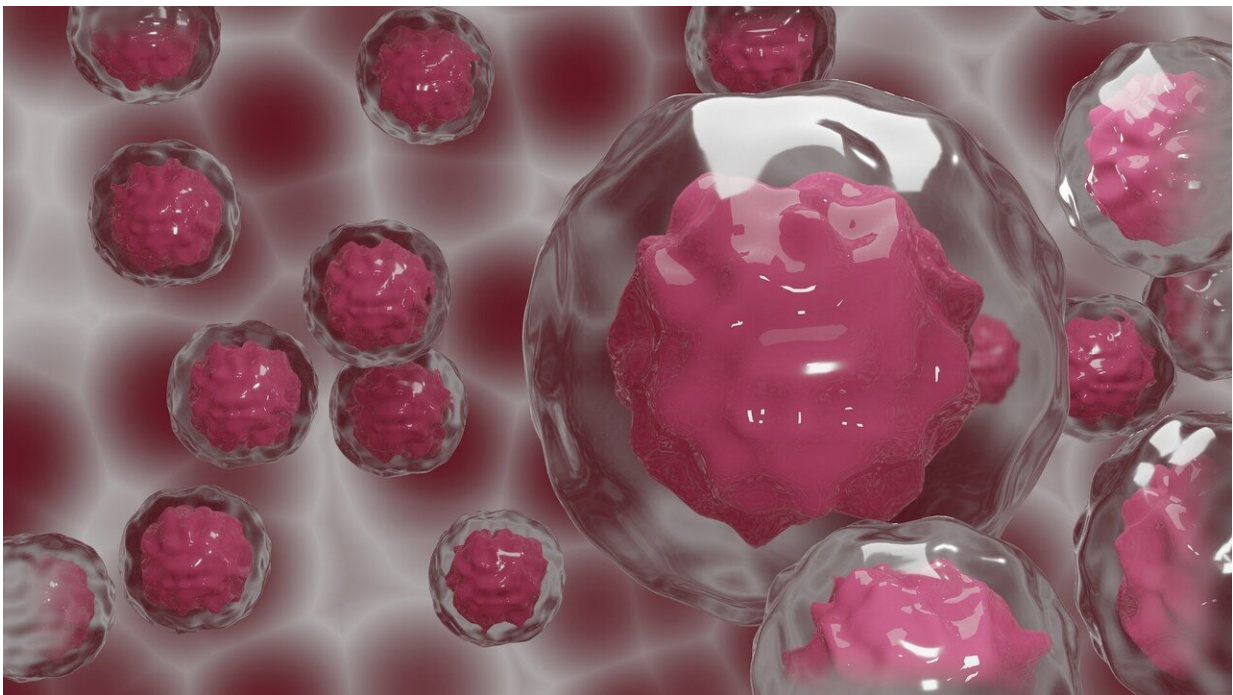


# New approach for cell therapy shows potential against solid tumors with **KRAS** mutations

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A new technology for cellular immunotherapy developed by Abramson Cancer Center researchers at Penn Medicine showed promising anti-tumor activity in the lab against hard-to-treat cancers driven by the once-considered 'undruggable' *KRAS* mutation, including lung, colorectal, and

pancreatic.

The study, published online in *Nature Communications*, successfully demonstrated using [human cells](#) that a T-cell receptor, or TCR, therapy could be designed to mobilize an immune system attack on mutated *KRAS* solid tumors and shrink them. The preclinical work has laid the groundwork for the first-in-human clinical trial now in the planning stages for the treatment of advanced pancreatic [cancer](#) in patients whose tumors harbor specific *KRAS* mutations and express a specific type of human leukocyte antigen, or HLA, the therapy is built to recognize.

"We've shown that targeting mutant *KRAS* immunologically is feasible and potentially generalizable for a group of patients with lung, colorectal and pancreatic tumors," said senior author Beatriz M. Carreno, Ph.D., an associate professor of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania and a member of the Center for Cellular Immunotherapies, the Abramson Cancer Center, and Parker Institute for Cancer Immunotherapy at Penn. "We look forward to taking this research to the next level and closer to [clinical study](#)."

*KRAS* mutations are among the most prevalent mutations observed in cancers and have been shown to drive tumor development and growth. Only recently have targeted therapies been shown to successfully treat a specific *KRAS* mutation found most commonly in lung cancer; however, no treatments currently exist for the majority of other *KRAS* mutations more prevalent in other tumor types. Immunological targeting of mutant *KRAS* represents an alternative treatment approach but has been less studied and understood.

Using a multiomics approach, the Penn team identified specific neoantigens associated with mutations at the G12 site on the *KRAS* gene. Neoantigens are protein fragments that form on the cancer cell surface

when certain mutations occur in tumor DNA. More than 75 percent of the alterations in the KRAS protein occur at G12, making it an ideal site to target with therapies.

Armed with this knowledge, the researchers tested a TCR therapy directed toward specific *KRAS* G12 [mutations](#) present in conjunction with particular HLA types highly prevalent among patients. They showed in a mouse tumor model that it was effective at attacking and eliminating tumor cells. HLAs are an important part of the immune system because they encode cell surface molecules that present specific neoantigens to the T-cell receptors on T cells.

In other words, HLAs are key genetic codes needed for these engineered T cells to find and attack tumors.

The research further supports the use of neoantigens for targeting [tumor](#) cells, for both cellular therapy and cancer vaccines, which have been underway at Penn Medicine and elsewhere.

Importantly, the neoantigen and HLA information from this latest study is being used to develop TCR therapies to treat [solid tumors](#), as well as new cancer vaccines. Based off these latest findings, the team initiated a vaccine clinical trial led by Mark O'Hara, MD, an assistant professor of Hematology-Oncology at Penn and co-author on the study, in pancreatic cancer targeting mutated *KRAS*.

The first clinical trial for the TCR [therapy](#) is projected to launch as soon as 2022, depending on regulatory approval, at Penn's Abramson Cancer Center for patients with advanced pancreatic cancer who have both the *KRAS* mutation and specific HLA types identified in this latest study—which could represent up to 10 percent of patients with pancreatic cancer. The study opens the door, however, to expand the patient population as researchers continue to discover more about the

neoantigens derived from regions of the *KRAS* gene and other mutated oncogenes implicated in driving cancer.

"We provide evidence that this oncogenic protein is a very promising clinical target of immune-based therapies," said lead author Adham Bear, MD, Ph.D., an instructor in the division of Hematology-Oncology at Penn and member of the Parker Institute for Cancer Immunotherapy at Penn. "The goal, now that we have identified these neoantigens and T cell receptors, is to translate these findings and apply them to develop new therapies at Penn."

Robert H. Vonderheide, MD, DPhil, director of the Abramson Cancer Center, and Gerald P. Linette, MD, Ph.D., a professor of Medicine in the Perelman School of Medicine, serve as co-authors.

**More information:** Adham S. Bear et al, Biochemical and functional characterization of mutant KRAS epitopes validates this oncoprotein for immunological targeting, *Nature Communications* (2021). [DOI: 10.1038/s41467-021-24562-2](https://doi.org/10.1038/s41467-021-24562-2)

Provided by Perelman School of Medicine at the University of Pennsylvania

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