

New combination therapy shows early promise against certain lung cancers

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Scientists at the Francis Crick Institute have found that using immunotherapy alongside a drug that blocks a common gene mutation in lung cancer could be a promising new combination therapy for certain

types of lung tumors.

Their work, published today (20 July) in *Science Advances*, could help select patients for clinical trials to confirm whether this combination therapy is effective in people.

Around 1.8 million people die from lung cancer each year, making it the leading cause of cancer death globally. While some people are effectively treated with immunotherapy, this does not work for most patients.

With only a quarter of people surviving more than five years after diagnosis, there is an urgent need to find new treatments or new combinations of existing drugs.

"In recent years, there has been a lot of attention on whether combining [immune checkpoint blockade](#), a type of immunotherapy, with a KRAS-inhibitor could be effective. This inhibitor works by blocking a mutated version of KRAS, a gene that helps control cell growth and death. As the mutation is present in about one third of lung cancer cases, it is a promising therapeutic target," explains Julian Downward, author and principal group leader and associate research director at the Crick.

In their study, the researchers tracked the effects of combining immune checkpoint blockade with KRAS inhibitors in mice. In tumors where there were already high numbers of active immune cells, so called "immune hot" tumors, the treatment successfully controlled the cancer. However, in cases where the immune system was not able to mount a strong response, the combination treatment was ineffective.

In 2021, the first KRAS-inhibitor was approved for use in non-small-cell lung cancer cases with the KRAS^{G12C} mutation. And there are various ongoing clinical trials exploring the effectiveness of combining this

inhibitor with immune checkpoint blockade.

However, most of these trials only involve patients who have already been through immune checkpoint blockade and have not responded. As [immunotherapy](#) has been unsuccessful, this suggests their tumors are not "immune hot" and so, according to this study, they are also unlikely to respond to the combination of treatments.

The researchers are calling for clinical trials to include patients with "immune hot" tumors, to ensure that the potentially effective combination is tested on those most likely to respond.

"KRAS inhibitors are very new so there's still a lot to learn about when they are most effective and which other treatments they can safely be combined with to give patients the best chance of living longer.

"Our study is an important part of this, suggesting that combining immune checkpoint blockade with a KRAS-inhibitor is likely to work in specific cancers. It is crucial this is factored into the design of future clinical trials," explains Miriam Molina Arcas, author and principal research scientist in the Oncogene Biology laboratory at the Crick.

The team also investigated the impact of the KRAS mutation on the tumor, the environment around the tumor and the immune system.

They found that, in lung cancer, mutated KRAS weakens signals which help activate the immune system while boosting hormone-like molecules which help create an environment that supports the tumor.

When they inhibited the mutated gene in mouse models, these pro-tumor effects did not occur. For example, within the tumor environment, there were fewer cells that suppress the immune system and more cytotoxic T cells which kill cancerous cells.

The KRAS gene is a member of the RAS family of genes which are implicated in about 20% of all cancers, including melanoma, bowel cancer and pancreatic cancer.

The scientists will continue their work studying the role of this family of genes in cancer, including researching ways it might be possible to stimulate the immune system to eliminate cancer cells that have developed resistance to RAS inhibitors.

More information: Edurne Mugarza et al, Therapeutic KRASG12C inhibition drives effective interferon-mediated anti-tumour immunity in immunogenic lung cancers, *Science Advances* (2022). [DOI: 10.1126/sciadv.abm8780](https://doi.org/10.1126/sciadv.abm8780).
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