

Researchers discover possible new treatment strategy for lung cancer

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Lung CA seen on CXR. Credit: [CC BY-SA 4.0](#) James Heilman, MD/Wikipedia

Lung cancer is the second most common cancer found in both men and women. It is estimated there will be roughly 228,000 new lung cancer cases this year, and nearly 30% of those patients will have mutations in the KRAS pathway. This type of mutation makes the cancer more aggressive and difficult to treat. Researchers at Moffitt Cancer Center are hoping to change that. In a new study published in *Cancer Research*, the team discovered a new treatment approach that may help this group of patients.

KRAS is a gene that regulates cell signaling in an "on" and "off" manner, leading to normal cell growth and division. Mutations that occur in the KRAS gene cause the protein to ignore any "off" signals that it receives, which results in unchecked cell growth. This is why researchers have been investigating areas in the KRAS pathway as possible therapeutic targets. For example, in melanoma, therapies that target the BRAF mutation, a protein in the KRAS pathway, have led to a positive patient response.

Moffitt researchers believe the MEK kinase, also found in the KRAS pathway, can be a possible target for [lung cancer](#) treatment. Through a series of drug screens, cell line and animal model experiments, they found that lung cancer [cells](#) treated with the MEK inhibitor trametinib in combination with the cytokines TNF α and IFN γ resulted in substantially more cell death than treating with a MEK inhibitor alone. TNF α was identified in the 1970s as Tumor Necrosis Factor but initial enthusiasm for using it in cancer treatment was quickly dampened by [inflammatory response](#) induced following TNF α administration, and the fact that most [tumor cells](#) resist killing by TNF α . In this study, the research team found that MEK inhibitors increase the number of receptors on the cell surface for TNF α to bind to, which leads to the delivery of a more potent and sustained cell death signal. IFN γ , a cytokine known to be crucial for anti-tumor immunity, further enhances the anti-tumor activity of MEK inhibitors and TNF α . Importantly, MEK inhibitors also considerably

increases expression of TNF α and IFN γ target genes, which can lead to increase in anti-tumor immunity.

"MEK inhibitors alone do not provide strong overall response for this group of patients," said Amer A. Beg, Ph.D., senior member of the Immunology Department and Lung Cancer Center of Excellence at Moffitt and lead author of this study. Beg and his team took their research further by investigating whether MEK inhibitors in combination with therapies known to increase expression of TNF α and IFN γ would provide a better response. They discovered that adding a PD-1 immune checkpoint inhibitor with MEK inhibitors resulted in the strongest tumor regression in mice. The researchers are planning further studies to combine MEK inhibitors with other immune therapies that provide strong expression of these cytokines in the tumor microenvironment, such as CAR T and adoptive T cell therapy approaches.

"These studies will help determine if modulation of the immune microenvironment along with tumor signaling is a viable treatment strategy for lung cancer patients with KRAS mutations and potentially other mutations that rely on MEK signaling," said Mengyu Xie, a cancer biology graduate student studying at Moffitt and a first author of the study.

"Demonstrating that an anti-[cancer](#) agent can so effectively modulate the activity of a cytokine signaling pathway crucial for so many biological processes is conceptually novel and can lead to new understanding of oncogenic pathways and strategies for targeting them" said Beg.

More information: Mengyu Xie et al, MEK inhibition modulates cytokine response to mediate therapeutic efficacy in lung cancer, *Cancer Research* (2019). [DOI: 10.1158/0008-5472.CAN-19-0698](https://doi.org/10.1158/0008-5472.CAN-19-0698)

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