

Researchers uncover a way to harness the power of immunotherapy for advanced prostate cancer

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Working in the Chinnaiyan Lab. Credit: University of Michigan Rogel Cancer Center

It's a scientific riddle tangled up in a complex web. How do you turn an immune cold cancer into one that responds to immunotherapy?

Researchers led by the University of Michigan Rogel Cancer Center started with a simple thread: an inhibitor that showed promise against metastatic castration-resistant [prostate cancer cells](#). This is the most challenging type of prostate cancer—advanced disease that has become resistant to hormone-based treatment.

From there, they continued to untangle the web to discover multiple levels of cellular processes that were preventing the [immune system](#) from mounting a response. Break past them with this inhibitor and suddenly what's considered an immune cold tumor turns red hot.

"Immunotherapy has dramatically improved outcomes for some types of cancer. But [prostate cancers](#) are typically immune cold, which means

these patients have benefited little from immunotherapies. Finding a way to rev up the [immune response](#) would create tremendous opportunity to improve patient outcomes," says Arul M. Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at Michigan Medicine. Chinnaiyan is senior author of the paper published in *Nature Cancer*.

Researchers started by screening a library of 167 inhibitors against prostate cancer cells. They found one, ESK981, had the most impact.

ESK981 is a class of drugs called multi-tyrosine kinase inhibitors, which are designed to hit multiple targets. This means it functions like a [combination therapy](#), able to block cancer on more than one front. It was originally developed to check [blood vessel growth](#) and has already been tested in phase 1 [clinical trials](#), which found it to be safe and well-tolerated.

In cell lines and mice with metastatic castration-resistant prostate cancer, researchers found ESK981 inhibited [tumor growth](#).

"The response was intriguing, but we wanted to understand the mechanism at play with ESK981 in prostate cancer cells," Chinnaiyan says.

They discovered several cellular processes were occurring. First was the role of a type of cell death called autophagy. The authors surprisingly found that ESK981 was a potent inhibitor of autophagy in [tumor cells](#). This caused the cancer cells to produce a protein called CXCL10, which led to recruitment of immune T cells to the tumor.

But there was one more layer to go. Ultimately, they traced it back to PIKfyve, a type of protein

called a lipid kinase. The authors discovered that ESK981 directly targets PIKfyve, affecting these multiple processes involved in metabolism and cell death.

The researchers confirmed this by knocking down PIKfyve in cell lines and mice. They saw the same processes occur: tumors stopped growing, autophagy was controlled and more T cells were recruited to the tumor. When they added an immune checkpoint inhibitor to the PIKfyve knockdown, the impact was even greater, significantly reducing tumors.

"Overcoming resistance to immunotherapy is an urgent need in prostate cancer. PIKfyve is a promising target, especially combined with an immune checkpoint inhibitor. This combination has potential to extend the benefit of immunotherapy to patients whose tumors have previously not responded," Chinnaiyan says.

Based on these findings, researchers have begun phase 2 clinical trials [using ESK981 alone](#) or [in combination with the immunotherapy nivolumab](#) for metastatic castration-resistant prostate [cancer](#).

More information: Autophagy inhibition by targeting PIKfyve potentiates response to immune checkpoint blockade in prostate cancer, *Nature Cancer* (2021). DOI: [10.1038/s43018-021-00237-1](https://doi.org/10.1038/s43018-021-00237-1), www.nature.com/articles/s43018-021-00237-1

Provided by University of Michigan

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