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When one drug fails, a new door opens for cancer treatment

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A new class of cancer drugs—called CDK4/6 inhibitors—recently approved to treat breast cancer can stunt the cancer's growth and replication. It is also being explored for a number of other cancers. Unfortunately, patients often develop resistance to the therapy, and the cause of that resistance has been difficult to pin down. Researchers at the Sidney Kimmel Cancer Center at Jefferson Health recently discovered the key resistance mechanism in prostate cancer and identified a molecular inhibitor that could help fight the disease when resistance develops.

"We provide evidence that a drug, already in development, could help fight the cancers that develop resistance to CDK4/6 inhibitors," said senior author Karen E. Knudsen, Ph.D., Director of the Sidney Kimmel Cancer Center at Jefferson Health. "This could potentially offer patients a more effective therapy to try when the CDK4/6 inhibitors fail."

The results were recently published in the journal *Clinical Cancer Research.*

In order to first explore how tumors become resistant to CDK4/6-inhibitor therapy, Dr. Knudsen and her team, including first author Renée de Leeuw, used a cellular model of prostate cancer that let them hone in on the process of resistance. The researchers found that as prostate cancer cells become resistant to CKD4/6-inhibitors they rewire the protein pathways essential for their survival. The transcriptome of the cancer cells fundamentally shifts. This rewiring causes the cells to

begin to depend on a different pathway for their growth, the MAPK-6 or MEK pathway, which normally does not play a big role in prostate cancer.

The researchers also showed, when the prostate cancers develop resistance to the CDK4/6 inhibitors and switch to being dependent on the MAPK-6 pathway, the cancer cells become much more aggressive, spreading and seeding metastases more rapidly in mouse models of the disease.

"However, this new dependence offers us an opportunity," said Dr. Knudsen. "MEK-inhibitors are currently being tested and in clinical trials. While these drugs show limited impact on earlier stages of disease they may become effective therapies as prostate cancer cells—and potentially other cancers as well—develop CDK4/6 resistance. By hitting cancer cells with one therapy, namely the CDK4/6 inhibitors, followed by a MEK inhibitor, we block the cancer's avenues of escaping death one by one."

MEK inhibitors have been approved for treating melanoma and are currently being tested for prostate cancer in clinical trials. But there are no currently open trials investigating the combination treatment with a MEK and CDK4 inhibitors together. "These studies will be instrumental in guiding the next generation of clinical trials with CDK 4/6 inhibitors in prostate cancer and gives us a strong rationale to target MEK pathway," said co-author W. Kevin Kelly, DO, Professor of Medical Oncology, Director of the Division of Solid Tumor Oncology, and leader of the Prostate Cancer Program at the Sidney Kimmel Cancer Center, which is recognized by the National Cancer Institute as one of eight Prostate Cancer Centers of Excellence.

More information: Renee de Leeuw et al, MAPK reliance via acquired CDK4/6 inhibitor resistance in cancer, *Clinical Cancer*

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Related clinical trial: www.clinicaltrials.gov/ct2/show/NCT02555189