Computational tool reveals untapped efficacy of cancer drug, leveling up cancer fight

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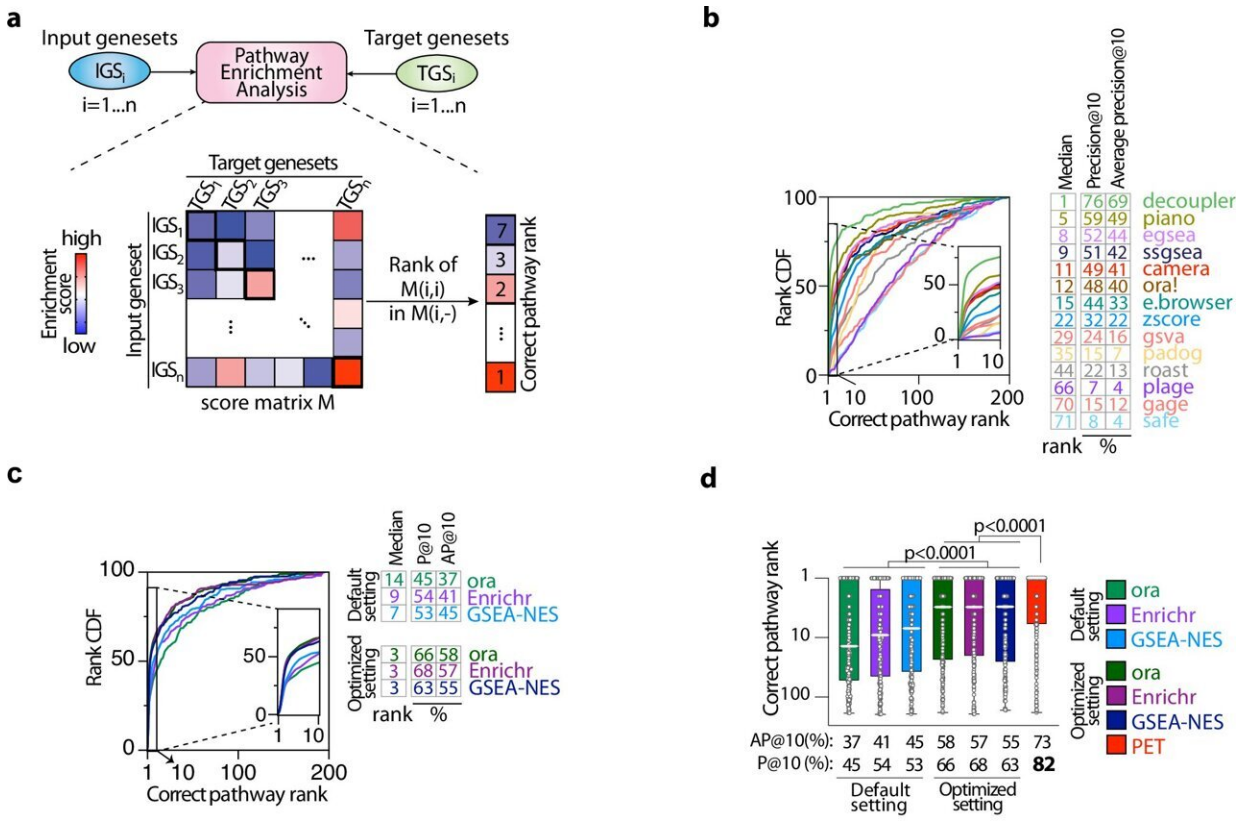

Benchmark for evaluating and optimizing existing pathway analysis methods. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-51859-9

Research from Purdue University in collaboration with the National Institutes of Health (NIH) reveals that, thanks to a new computational

tool, a cancer drug dismissed by traditional testing methods may be effective in treating bladder cancer.

Called the Pathway Ensemble Tool (PET) and described in research published Aug. 24 in *Nature Communications*, it accurately identifies the most important biological pathways disrupted in cancer and other complex diseases, enabling precise treatment strategies. Biological pathways are the series of steps that molecules take within cells to accomplish specific tasks such as cell growth or energy production.

PET is a novel combination of multiple existing techniques. It was developed by Majid Kazemian, associate professor of biochemistry in the College of Agriculture and computer science in the College of Science at Purdue and member of the Purdue Institute for Cancer Research (PICR). Kazemian worked with Behdad Afzali, the Earl Stadtman Investigator at the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH.

"We conduct large studies using massive amounts of experimental data to determine how well different tools can find pathways related to diseases such as cancer," Kazemian said. "Surprisingly, we found that the commonly used tools—even though people have tried to make them work well—didn't do as well as expected in finding important cancer-related pathways.

"We developed PET, which statistically combines optimized versions of different tools to get much better results. It's robust and reliable, and it helps us accurately determine which pathways are malfunctioning in cancer without bias, enabling more precise drug identification."

The research teams used PET to identify dysfunctional biological pathways in 12 different types of cancer. They discovered numerous pathways associated with individual cancers as well as several that

signaled either a high or low risk of cancer progression, effectively acting as potential biomarkers of outcomes.

"These biomarkers are crucial for selecting appropriate treatments because they signal when someone has a high risk of death from cancer, even if detected early, and can serve as drug targets," Kazemian said. "We used PET-derived pathways for drug prediction and discovered effective known and novel drugs that were previously missed using the standard methods of analysis."

The researchers found that pathways disrupted in bladder and cervical cancers share many genes affected by the enzyme CDK9. When they tested a drug that blocks CDK9, they found that the drug inhibits bladder and cervical cancer cell growth in lab and animal tests more effectively than previous evaluation tools had indicated.

In a test specific to bladder cancer, PET determined that the CDK9-inhibitor drug called CCT068127 was more effective at slowing cancer-cell growth than other drugs tested. This finding was unexpected, as previous researchers had not identified CDK9 as a target for bladder cancer.

The finding has led to a new clinical trial involving fellow PICR affiliate Deborah Knapp, Distinguished Professor of Comparative Oncology at Purdue. She is working to study the efficacy of the clinically available CDK9 inhibitor in dogs with bladder cancers that are similar to human bladder cancers.

"We anticipate that our findings will allow for the development of improved pathway discovery tools similar to PET," Kazemian said. "This will lead to tangible insights into disease mechanisms and identify novel diagnostic markers and prognostic markers, and therapeutics for cancer."

More information: Luopin Wang et al, Unbiased discovery of cancer pathways and therapeutics using Pathway Ensemble Tool and Benchmark, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51859-9

Provided by Purdue University