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New tool uses 'drug spillover' to match cancer patients with treatments

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Kinase Addiction Ranker (KAR) mines drug and cancer cell data to pinpoint drivers of disease and recommend treatments. Credit: Flickr/Justin Grimes cc license.

Targeted therapies attack a cancer's genetic sensitivities. However, it can be difficult to discover the genetics driving a patient's cancer, and the effects of drugs designed to target a genetic abnormality often go beyond their intended target alone. The result is threefold: sometimes a drug is prescribed to treat a target that proves to be irrelevant to the disease, sometimes an existing drug could be used to treat a cancer for which there is no approved targeted therapy, and sometimes a combination of targeted treatments could be used to simultaneously silence more than one genetic cause of a patient's cancer.

A recent article in the journal *Bioinformatics* from researchers at the University of Colorado Cancer Center describes a new tool that improves the ability to match drugs to disease: the Kinase Addiction Ranker (KAR) predicts what genetics are truly driving the cancer in any population of cells and chooses the best "kinase inhibitor" to silence these dangerous genetic causes of disease.

"For example, we know that the disease Chronic Myeloid Leukemia is driven by the fusion gene bcr-abl and we can treat this with the tyrosine kinase inhibitor imatinib, which targets this abnormality. But for many other cancers, the genetic cause and best treatments are less distinct. The KAR tool clarifies the drug or combination of drugs that best targets the specific genetic abnormalities driving a patient's cancer," says Aik Choon Tan, PhD, investigator at the CU Cancer Center, associate professor of Bioinformatics at the CU School of Medicine, and the paper's senior author.

KAR makes its predictions based on two data sources. First is data describing the full spectrum of effects of the drugs known as tyrosine kinase inhibitors (TKIs).

"A lot of these kinase inhibitors inhibit a lot more than what they're supposed to inhibit. Maybe drug A was designed to inhibit kinase B, but

it also inhibits kinase C and D as well. Our approach centers on exploiting the promiscuity of these drugs, the 'drug spillover'," says Tan.

For example, the drug crizotinib was designed, tested, and approved to silence the ALK-EML fusion gene that drives a subset of lung cancers, but also happens to act against a similar rearrangement of the ROS1 gene. The *New England Journal of Medicine* reports the successful treatment of patients with ROS1 rearrangement, with the drug crizotinib. In this case, what researchers and doctors first called an "ALK inhibitor" turns out to have other, important uses. And, in fact, for each drug in this class of kinase inhibitors, there is a profile or signature describing the few or many kinases each drug fully or partially inhibits.

Tan and colleagues combine these kinase inhibition signatures with the results of high-throughput screening - a method for testing hundreds of drugs against a panel of cancer cells. Specifically, Tan used the publicly available Genomics of Drug Sensitivity in Cancer database to discover which compounds have been shown to be active against which cancer cell lines.

The result is KAR, which does two things: for any cancer cell line, like those derived from a patient with cancer, the program ranks the kinases that are most important to the growth of the disease; then the program recommends the combination of existing kinase inhibitors drugs (TKIs) that is likely to do the most good against the implicated kinases.

The recent paper describes the success of the KAR tool. First, based on samples from 151 leukemia patients, KAR was able to correctly predict the outcomes of patients treated with certain drugs. The same was true in 21 lung cancer cell lines - KAR predicted the degree of sensitivity of these cells to certain drugs, matching the results of experiments that show these sensitivities. Finally, the researchers asked KAR to rank the kinases most important to the proliferation of the lung cancer cell line

H1581 and to recommend a combination of targeted treatments to attack these cells. KAR suggested the combination of ponatinib with experimental anti-cancer agent AZD8055, and, in fact, this combination proved highly effective at controlling these cells, creating what the researchers call a "synergistic reduction in proliferation."

"This is a new tool, a new way of looking at drugs and how we combine drugs to target kinase dependency in cancer," Tan says.

More information: *Bioinformatics*, bioinformatics.oxfordjournals. … ormatics.btv427.long

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