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Drug-target database lets researchers match old drugs to new uses

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There are thousands of drugs that silence many thousands of cancer-causing genetic abnormalities. Some of these drugs are in use now, but many of these drugs are sitting on shelves or could be used beyond the disease for which they were originally approved. Repurposing these drugs depends on matching drugs to targets. A study recently published in the journal *Bioinformatics* describes a new database and pattern-matching algorithm that allows researchers to evaluate rational drugs and drug combinations, and also recommends a new drug combination to treat drug-resistant non-small cell lung cancer.

"Most cancers have more than one genetic alternation. And even genetically targeted drugs tend to affect more than only their stated target. And so the challenge is matching drugs with many effects to cancers with many causes in a way that best maps the drugs' effects onto the intended targets," says Aik Choon Tan, PhD, investigator at the University of Colorado Cancer Center and associate professor of Bioinformatics at the CU School of Medicine.

There are about 500 kinases in the human genome, each of which represents a potentially important drug target. Tan describes the database as a spreadsheet with 500 columns, each column representing a kinase. Heading each row is a drug and then in each column cell is that drug's activity against the kinase.

"Imagine you know a cancer is caused by five kinases acting in unison," Tan says. "Our approach would allow you to query the database for this

pattern and discover the drug or combination of drugs that best match the genetic needs."

Because many of these drugs have already earned FDA approval for use in other diseases, the processes of repositioning these drugs for new diseases is much less involved and expensive than if drug developers had started fresh.

Tan and colleagues put the technique to use to recommend drugs that could turn off the kinases that non-small cell lung cancer uses to create resistance existing treatments. It's been an important question – many lung cancers depend on over-activation of the gene EGFR, but then when EGFR inhibitors like gefitinib or erlotinib are used, the cancers tend to activate other "kinases" that allow the cancer to by-pass around this dependence. Tan and colleagues asked what are these kinases that allow lung cancer to evade gefitinib, and what other drug might turn them off.

The answer may be in the drug bosutinib, developed by Pfizer, which earned FDA approval in 2013 for the treatment of chronic myeloid leukemia. The drug out-competes the body's energy source, ATP, for space in kinases and so keeps them from being activated. And it turns out that bosutinib may inhibit the activity of exactly the kinases that EGFR-dependent lung cancers need to mutate around the challenge of EGFR inhibitors.

In tests on EGFR-dependent lung cancer cell lines, Tan and colleagues show that the drugs gefitinib and bosutinib "showed additive and synergistic effects."

In a mechanism that Tan hopes will become common, his group will now hand off this rational combination to other researchers at the CU Cancer Center and elsewhere who will move the drugs toward a human clinical

trial.

More information: The K-Map database is online and free for use at tanlab.ucdenver.edu/kMap/

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