New method to measure how drugs interact

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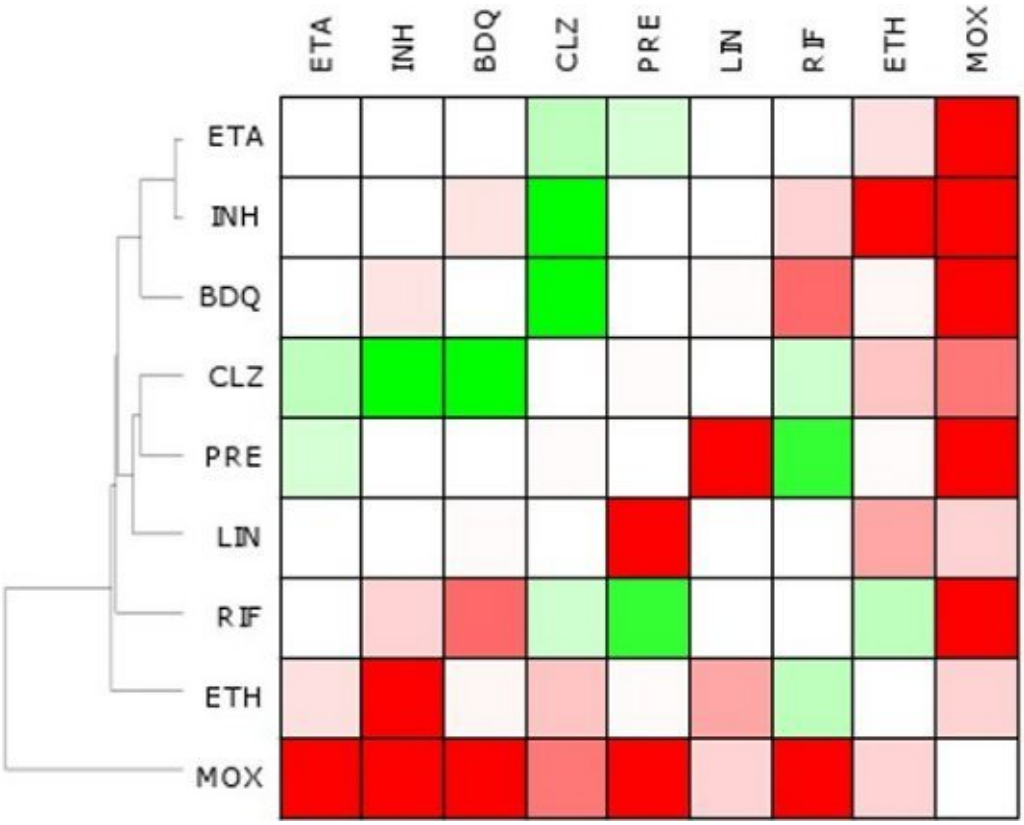

Drug interactions are measured by the shape of the contour on a checkerboard of dose combinations. “Studying such interactions is challenging because of the sheer number of combinations,” said Bree Aldridge. Credit: Cokol et al., Sci. Adv. 2017;3: e1701881

Cancer, HIV and tuberculosis are among the many serious diseases that are frequently treated with combinations of three or more drugs, over

months or even years. Developing the most effective therapies for such diseases requires understanding how combining drugs affects their efficacy.

If drugs reinforce one another, that synergy may be enough to lower the doses required, potentially relieving side effects, reducing treatment time, and improving patient quality of life. But if drugs work against each other, efficacy will be reduced.

Now researchers at Tufts, along with colleagues at Harvard University and Turkey's Sabanci University, have developed a new method to measure how drugs act in combination. The new methodology is more efficient and less expensive than traditional testing, and provides a framework for systematic testing of any dose-dependent therapeutic agent.

"Identifying synergies early in the pre-clinical drug development process can help us prioritize drug combinations for further development," said Bree Aldridge, assistant professor of molecular biology and microbiology at Tufts School of Medicine and adjunct assistant professor of biomedical engineering. "But studying such drug interactions is challenging because of the sheer number of combinations and the current method of measurement."

Such testing has traditionally been done on pairs of drugs through a "checkerboard" methodology using an iPhone-sized plate containing a grid of tiny wells, typically 96 or 384 wells. A bacterium—or other target organism—is placed into each well along with a carefully calibrated dose of the two drugs in varying strengths. Bacterial growth in each well is measured to determine its response to the drugs.

The complexity and cost of testing increase exponentially with the number of drugs being examined. To determine synergy of five drugs

would require measuring 100,000 cell response combinations on 1,000 plates. As a result, combinations of more than two drugs—called high-order combinations—rarely undergo such testing.

The new method, though, doesn't require an exhaustive analysis of all cell behaviors in all possible dose combinations. Instead, in order to predict which high-order combinations are most likely to be synergistic, it targets only the most information-rich drug-dose combinations.

In experiments using Mycobacterium tuberculosis, the bacterium that causes tuberculosis, Aldridge and her collaborators found that measuring only certain wells in the grid mirrored the results obtained by testing all the wells.

Aldridge uses the analogy of assessing metropolitan rush hour traffic. "Instead of monitoring traffic in every neighborhood and on every road, if you look at traffic at multiple key points—such as the Mass Turnpike and the airport tunnels in Boston—you'll be able to get a pretty good picture of whether commuting will be a breeze or a nightmare."

The new proof-of-concept study, recently reported in the journal *Science Advances*, analyzed pairwise and combination interactions among nine drugs now used against M. tuberculosis. Aldridge, whose work merges molecular and mathematical approaches to the study of mycobacteria, hopes to test additional drugs in future studies of the method, which is dubbed DiaMOND (diagonal measurement of n-way drug interactions).

The paper's first and co-corresponding author along with Aldridge is Murat Cokol, former visiting scientist in the Aldridge laboratory and the Laboratory of Systems Pharmacology (LSP) based at the Harvard University School of Medicine, where Aldridge is also an investigator. Other authors are Nurdan Kuru, of Sabanci University in Turkey; Ece Bicak, who formerly worked with Cokol at LSP; and Jonah Larkins-

Ford, a Ph.D. student in molecular biology and microbiology at the Sackler School of Graduate Biomedical Sciences at Tufts.

Aldridge stresses that drug synergy should be only one consideration in developing effective patient therapies. "Synergies observed in the lab are not always associated with optimum clinical treatments," she said.

For example, it may make sense to include less synergistic combinations in a regimen in order to help combat drug resistance. But, she added, "DiaMOND can play an important role by enabling us to do a much better job of identifying potentially valuable synergies among candidate drugs in the pipeline."

More information: Murat Cokol et al. Efficient measurement and factorization of high-order drug interactions in Mycobacterium tuberculosis, *Science Advances* (2017). DOI: 10.1126/sciadv.1701881

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