Curve ball: New approaches, surprising results challenge fundamental principle of drug discovery

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Credit: AI-generated image (disclaimer)

(Phys.org) —After analyzing hundreds of interactions between cancer drugs and cancer cells using information theory and advanced modeling techniques, Harvard Medical School researchers have found that a standard model for predicting drug effectiveness is incomplete and

potentially misleading.

The findings, published recently in *Nature Chemical Biology*, could have implications for directing billions of dollars of drug research in a way that will rule out drugs unlikely to be effective in the clinic and highlight potentially useful drugs that the traditional standard would miss. The techniques suggested by the findings could also potentially help identify combination therapies that would boost the performance of under-achieving drugs and help clinicians maximize effectiveness without undue side effects.

"The results of this study are a small but significant step toward a new understanding of therapeutics," said senior author Peter Sorger, the Otto Krayer Professor of Systems Pharmacology and head of the HMS Program in Therapeutic Science.

Trying to predict the interaction of thousands of cells in a body with thousands of drug molecules is like watching a dozen games of billiards all at once and trying to predict where the balls will all end up. Each single ball bouncing off another follows simple, precise physical rules that play out in unpredictable ways in an enormously complex environment.

In biochemistry, researchers use mathematical relationships to predict how a given drug will perform in a particular set of circumstances. One standard rule states that for any drug, the relationship between effectiveness and dosage can be drawn as a sinuous sigmoidal curve in the characteristic shape of an elongated italic S.

In a typical graph comparing a variety of drugs, the good ones—the ones that kill lots of cancer cells at doses with few toxic side effects, say—cluster on the left, and less effective drugs cluster on the right (meaning that more drug is needed to achieve similar effect).

"The shape of this curve and the particular mathematical relationship between dosage and effectiveness that the curve represents have been held as a fundamental principle of biochemistry for more than a century," said Sorger. The relationship is used to measure all kinds of natural and therapeutic biochemical reactions, from drugs killing pathogens to signals binding with receptors.

"It's like the hydrogen ion in physics—that most basic particle upon which we build our science. Except it turns out we have focused on one variable to the exclusion of other, equally important ones," Sorger said.

The most widely used measure of drug sensitivity in both industry and academia is the canonical S-shaped dose-response curve. Conventionally, scientists evaluate these curves based on a single parameter, potency. In the case of cancer drugs, it's the concentration of the drug needed to kill half the cancer cells in a sample. According to the theory, the rest of the curve can be described using that single metric.

Mohammad Fallahi Sichani, HMS research fellow in systems biology, wanted to see what would happen if the drugs were evaluated using other parameters. Would the points line up as predicted? Do the parameters all correlate in real life?

Using previously published data, the team evaluated the effectiveness of 64 anticancer drugs on 53 well-characterized breast cancer cell lines. About one-third of the curves looked as expected, but most were much flatter, with very gentle increases in effectiveness with increasing dosage. Others plateaued at partial effectiveness, with a large fraction of cancer cells surviving at even the highest doses.

In multiple-generation tests of drugs that worked against only a subset of the cells in the sample, surviving daughter cells showed the same uncharacteristic response curves as their predecessor cells, an

observation that ruled out the possibility that a portion of the population in the initial test had evolved resistance to the drugs or that there were heritable genetic differences among the population.

"We find that non-canonical drug responses arise from cell-to-cell variability," Fallahi-Sichani said. By reporting on the population average, classical dose-response curves hide variation between the susceptible and resistant cells within genetically matched populations.

The single-cell experiments suggested that the relative effectiveness of the drug on different cells was related to different levels of proteins within particular cells or to random variations in the micro-structures within the cells. In clinical cases, this variation would be compounded by the physical differences between regions of tumors, vascularization and a number of other factors.

Finding a path to the potential benefits of new understandings of how drugs work will depend on changing the criteria we use to evaluate drug efficacy, the researchers said. Rather than concentrating only on finding potent drugs, discovery should also evaluate the incremental benefit of increasing dose (the slope of the curve) and the fraction of cells affected.

"If you do not evaluate potential new drugs on this basis, you miss ways to improve how drugs work in patients," Sorger said. At the same, Sorger and Fallahi-Sichani emphasize that it will be important to verify their findings with a larger range of drugs and using primary human cancers.

More information: www.nature.com/nchembio/journa … l/nchembio.1337.html

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