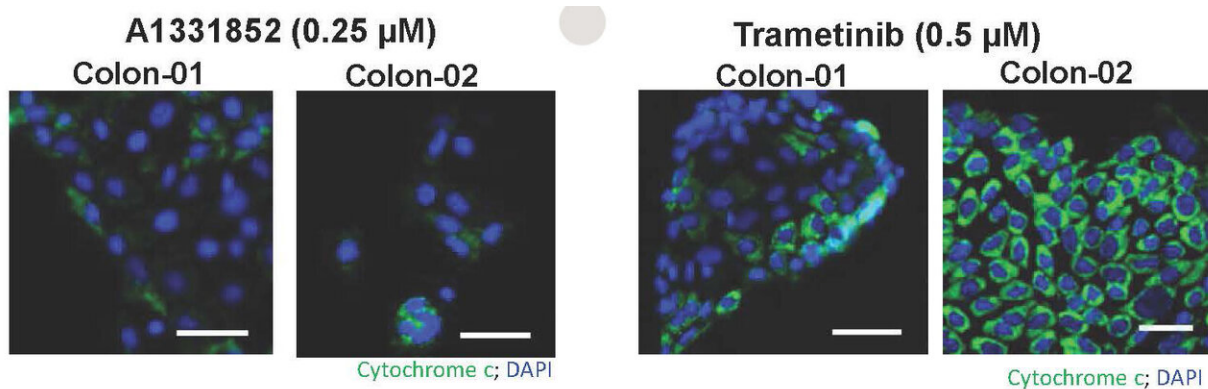# New technique may quickly and accurately predict effective therapies in solid tumors

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Using a small panel of drugs, the researchers found that the compounds A1331852 and trametinib increased the death of cancer cells in human colon tumors. Credit: P. Bhola et al., *Science Signaling* (2020)

A new method of screening thousands of drugs in freshly collected human tumor cells can help identify which of the drugs are most likely to be effective against those cancers, Dana-Farber Cancer Institute researchers report today in a study published in *Science Signaling*.

Because the technique uses tumor cells that less than a day earlier were in patients' bodies, it may well prove more accurate than traditional drug -screening approaches, which use laboratory cell models that may be weeks or even years removed from their origin in patients, the study

authors say. Its use could improve physicians' ability to personalize treatment to individual patients and help scientists uncover vulnerabilities in cancer cells that can be targeted by new drugs.

"Cancer cells that are cultured for extended periods of time can undergo a variety of changes and may not be representative of the tumor cells that are actually in a mouse or human," says study first author Patrick Bhola, Ph.D., of Dana-Farber. "The challenge has been to create a drug-screening technique that shrinks the gap between tumor cells in the body and the cells we do the screening on. The technique we've developed helps to accomplish that."

The technique, known as high-throughput dynamic BH3 profiling (HT-DBP) is a scaled-up version of a test created by Dana-Farber researchers that gauges how close tumor cells are to death after treatment with cancer drugs. Death in this case is defined as apoptosis—the self-destruct mechanism that cells initiate in response to DNA damage and many cancer therapies.

When many chemotherapies are applied to cancer cells, they change the balance of pro-death and anti-death molecules at mitochondria—structures best known for providing energy to the cell. Once the activity of pro-death molecules outweighs the activity of anti-death molecules, mitochondria release toxic substances that destroy the cancer cell. To determine how close the cell is to the brink of apoptosis, a property scientists have dubbed "apoptotic priming," researchers add segments of pro-death proteins to mitochondria and directly measure the release of toxic proteins. The segments are known as BH3 domains, hence the name "dynamic BH3 profiling" or DBP.

When a drug is put on a patient's cancer cells, DBP indicates whether, and how fully, the drug switches on the pro-death program. Tumor cells that show a significant increase in apoptotic priming after being treated

with a particular drug are likely to respond to that drug in the lab as well as in patients.

One of the virtues of the first version of DBP was that it generated results quickly—less than a day in many cases. But it was limited by its ability to screen only 10-20 drugs at a time—a significant constraint given the myriad drugs now available to treat many kinds of cancer. Dana-Farber researchers joined colleagues at the Broad Institute of MIT and Harvard and the Laboratory of Systems Pharmacology at Harvard Medical School to miniaturize and automate DBP so it could screen hundreds or thousands of drugs, creating a high-throughput (HT) model of the technique.
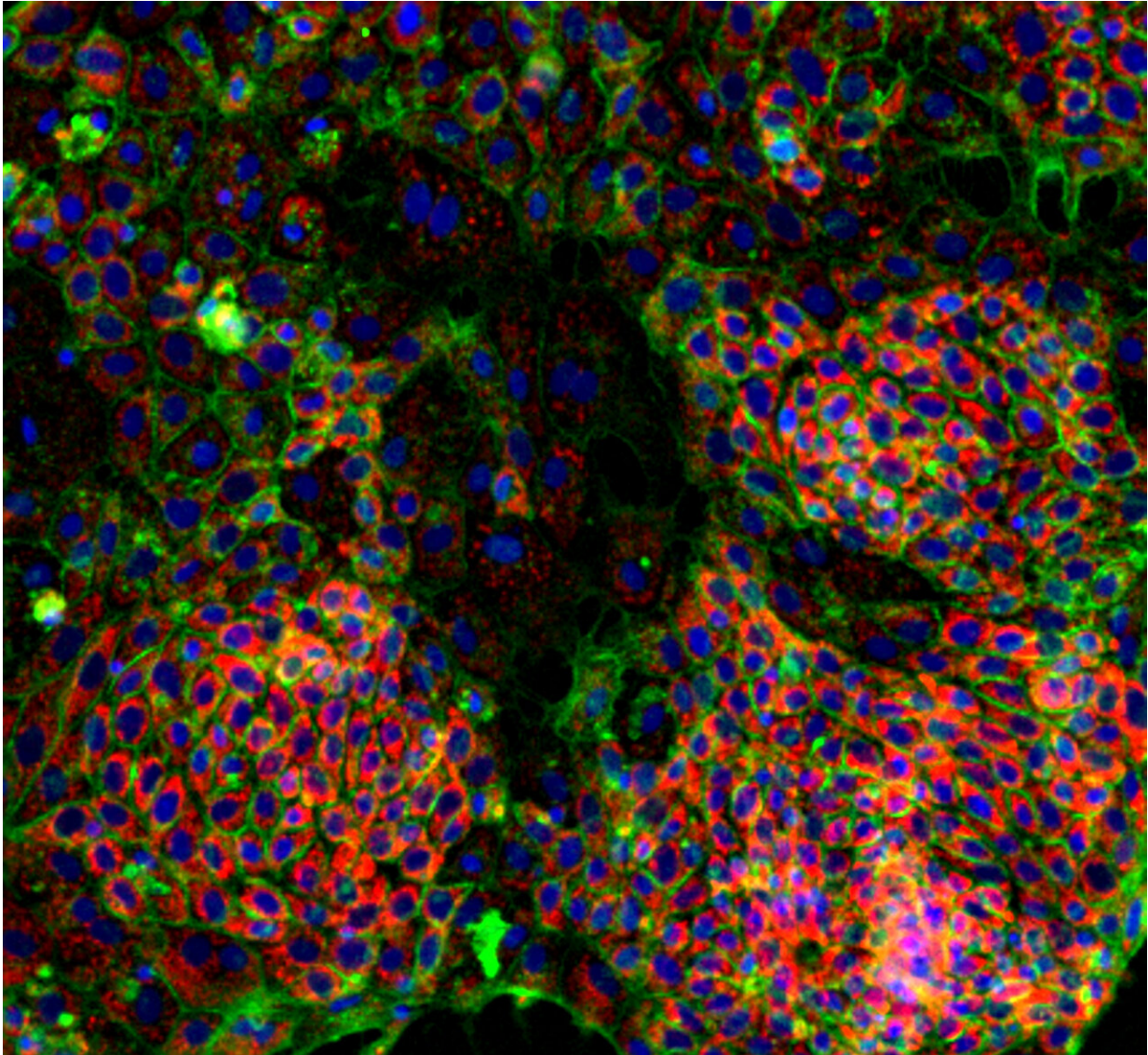
Image of colon cancer cells from a primary resected human colon tumor after 24 hours of ex vivo culture. Prior to imaging, cells were subjected to high throughput dynamic BH3 profile, which measures induction of apoptotic signaling after a brief 24-hour exposure to drugs. Nuclei are marked by Hoechst 33342 (blue), human EpCam Alexa Fluor 488 (green), and cytochrome c Alexa Fluor 647 (red). Credit: Patrick Bhola & Anthony Letai

The increased capacity meant investigators could conduct "unbiased"

screenings drugs in patient or mouse tumor cells—screenings not influenced by any preconceptions of which agents might perform best, and therefore completely objective.

HT-DBP can be used as both a scientific tool and a means of rapidly matching patients with the drugs best able to corral their cancer. In the *Science Signaling* study, researchers used HT-DBP to screen 1,650 drugs in fresh samples of breast cancer tissue from mice. They selected six of the drugs—three that showed activity in DBP and three that did not—to test in the mice. They found that the three that had been flagged as active caused the animals' tumors to shrink or delayed tumor growth. The three that had shown no signs of activity on DBP, by contrast, had no discernible effect on the tumors. The researchers also performed similar screens on mouse avatars of colorectal cancer and identified a drug combination that delayed tumor growth in one of the mouse models.

These results point to the advantages of performing direct functional drug testing on freshly isolated tumor tissue, the study authors say. "Laboratory specimens of tumor tissue are widely used to extract information on the molecular makeup of tumors—the DNA, RNA, proteins, and other components of cells," says Dana-Farber's Anthony Letai, MD, Ph.D., the new study's senior author. "While these studies have had a major impact on cancer treatment, they provide a static picture of the tumor cell, rather than the kind of functional information we need to understand how tumor cells actually interact with drugs. Our approach involves putting living cancer cells in contact with drugs to assess their potential."

The investigators also explored whether tumor cells grown in culture conditions for an extended period of time differed from fresh cells in their vulnerability to specific cancer drugs. To evaluate the effect of extended culture on tumor cells, the investigators performed HT-DBP on

freshly collected tumor cells from breast cancer tissue from mice, and on tumor cells from the animals that had been grown in a lab for a month. They found that while some drug vulnerabilities were preserved during the extended culture, other vulnerabilities were artificially lost or gained. Importantly, a drug vulnerability that was lost during extended culture was able to delay tumor growth in mice, whereas a vulnerability that was gained during extended cultured had no effect on the tumors. These results suggest that performing drug screens on extended cultures of cancer cells may miss potentially useful therapies.

The technique, when applied to patient tissue, could be used to personalize therapy and improve the translation of therapies from the bench to the bedside. "With HT-DBP, the drug could be screened on a tumor sample only recently removed from a patient," Letai says. "By using tissue samples with greater fidelity to tissue within the body, this technique provides a more accurate representation of what actually happens when a drug meets a tumor."

To evaluate its potential in customizing treatment, investigators performed HT-DBP on colon cancers directly removed from patients, rather than ones that had first been cultured in a lab or modeled in a mouse. The test identified several agents that increased apoptotic signaling in human colon cancer cells, making them potential candidates as treatments for the cancer.

The technique could be used in clinical trials to identify patients most likely to benefit from investigational therapies, researchers say. It can also be used in the lab to gain insights into the molecular workings of cancer cells. If HT-DBP reveals that a drug targeting a particular signaling pathway that pushes a set of tumor cells toward apoptosis, it's a sign that the cells are depending on that pathway for their growth and survival.

More information: "High-throughput dynamic BH3 profiling (HT-DBP) may quickly and accurately predict effective therapies in solid tumors," *Science Signaling* (2020). stke.sciencemag.org/lookup/doi … 26/scisignal.aay1451

Provided by Dana-Farber Cancer Institute