

Fred Hutch Study Finds New Life for “Ineffective” Drugs

Innovative method using more authentic tumor samples reveals untapped potential for drugs written off by more conventional tests.

October 6, 2025 By Fred Hutch News Service and John Higgins

Pharmaceutical companies typically test drugs on isolated cancer cells cultured under ideal conditions in a Petri dish.

Cancer cells in living organisms, however, thrive within a [tumor microenvironment](#), or TME, that includes host cells, immune cells, molecules, and blood vessels that cancer hijacks to thwart their normal anti-tumor functions.

Cancer shapes the TME and vice versa, presenting many potential therapeutic targets, but testing drugs at scale on cancer cells embedded in their TME poses many practical and technological challenges.

A new study by Fred Hutch Cancer Center systems biologist [Taran Gujral, PhD](#) and his colleagues compares the effectiveness of drugs tested on two different kinds of samples: the conventional cancer cells grown in a Petri dish and on samples Gujral calls “microtumors,” which comprise thin slices of tumor that contain cancer cells but also key elements of the TME.

They tested 31 drugs on microtumors and then used those results to train a computer model to predict the likely responses of more than 400 additional compounds.

The study, [published last week in the journal Cell Reports Medicine](#), shows that some drugs that work well in Petri dishes (a two-dimensional environment) work less well on the more authentic microtumors (a three-dimensional environment).

Surprisingly, the model predicts that three times as many drugs, on average, would be effective against 3D microtumors than they would against conventional cancer cells grown in Petri dishes. That was unexpected because cancer cells double quickly under 2D culture conditions, which should be ideal for drugs that target rapid growth.

“We always thought that you will find more drugs that will work in 2D than in 3D,” said co-first author, [Nao Nishida-Aoki, PhD](#), a former postdoctoral fellow with Gujral’s lab in the [Human Biology](#)

[Division](#). “But the really surprising factor here for us was it’s actually the other way around.”

She now runs her own project at the Waseda Institute of Advanced Study at Waseda University in Tokyo.

In the second part of their study, they focused on one promising drug revealed by the screen — doramapimod, or dora — which they confirmed didn’t work on cancer cells in a dish, but did work on microtumors.

Dora is better known for its potential to combat rheumatoid arthritis, but by figuring out how dora worked, Gujral’s team gained new insights into how the TME supports cancer.

Their discovery suggests that many drugs initially written off as ineffective by traditional 2D screens using cultured cancer cell lines may have untapped potential that could be realized with a better understanding of the complex relationship between cancer and the TME.

“For all these decades, we’ve been screening drugs in 2D,” Gujral said. “We could be missing many things.”

Making the most of microtumors

Cancer cell lines that can grow and divide perpetually in a lab, such as the famous [HeLa cell line established in 1952](#), have powered generations of biomedical research and [prompted much debate](#) and enduring policy changes about consent and privacy.

Such cell lines are called “immortal” because they can grow endlessly in culture, providing a long-lasting, plentiful and cost-effective platform for big experiments that produce lots of data.

But testing drugs only on isolated cancer cells misses the cocoon that surrounds cancer in a living organism — the TME — which includes non-malignant host cells and immune cells as well as non-cellular components such as blood vessels and molecules that relay growth signals and provide structure for the tumor and its niche in the body.

The TME co-evolves with a tumor and creates workarounds to therapies that inhibit cancer’s growth and spread, sending clinicians back to the drawing board when it becomes resistant.

“The tumor is not just made up of cancer cells,” Gujral said. “Drugs can work in a Petri dish, but they don’t necessarily work in vivo in mice or in humans. That’s because the environment is very different.”

Gujral and other researchers have developed a new model system for research and drug testing outside of the body that more closely resembles how cancer cells live within the body.

The approach stacks thin tumor slices that include key elements of the TME to create what Gujral calls “microtumors,” which can be prepared quickly from fresh tumor samples.

Microtumors more authentically represent cancer in its native environment, but they are short-lived and can't be produced in the quantities necessary to support big experiments the way conventional cell lines do.

To make the most of their short-lived and limited supply of tumor slices, Gujral's team tested a small number of drugs known to block the activity of enzymes called kinases, which help regulate cell growth, division, metabolism and survival.

They then used the results to train a computer model to predict how more than 400 other kinase inhibitors in various stages of development for clinical use, including drugs already approved by the FDA, would likely respond.

"The drugs we found that work in 2D, they also work in 3D, but there were some quantitative differences," Gujral said.

For example, if a drug reduced cancer cell growth by 50% in a 2D model, it might reduce growth by only 40-45% in a 3D model.

"It still worked, but not as effectively," Gujral said.

They were astonished to discover, however, that the model predicted that three times as many drugs are likely to work on 3D microtumors than on conventional 2D cell lines cultured in a Petri dish.

"It's possible that those drugs are targeting other cells that are not present when you're just growing cells on Petri dish and it's also possible that those drugs target cancer cells that are in a different state now," Gujral said.

In the Petri dish, isolated cancer cells get plenty of food and grow under ideal conditions. But in their natural state embedded in the TME, they may be under more stress competing with other types of cells, which may make them more vulnerable to drugs than they would be in the Petri dish.

The team selected a dozen of the drugs predicted to do better in a 3D microtumor and put them to the test in three different mouse models. One drug stood out as particularly promising: —
doramapimod.

"Dora is a drug that actually passed a safety trial in humans and went into clinical trials for non-cancer things such as rheumatoid arthritis and other indications, but it did not pass the efficacy trial," Gujral said. "It's a drug that's safe, but it has never been tested in cancer before because in 2D models it doesn't work."

But somehow dora does make a difference with microtumors and Gujral's team wanted to find out why.

Exploring the TME with dora

“The first thing we checked is whether dora works on cancer cells. No, it doesn’t kill cancer cells,” said Songli Zhu, PhD, lab manager for the [Gujral Lab](#) and a co-first author of the study. “And then we looked at what dora does to tumors.”

They discovered that in tough, fibrous tumors, dora makes the TME less hospitable for cancer by decreasing the production of complex molecules that help hold the TME together.

“We found out that it doesn’t change a whole lot of genes in the tumor, except it changes collagens or what we call extracellular matrix proteins,” Gujral said.

That was interesting because the extracellular matrix holding the TME together can shield cancer cells from the effects of immunotherapy or chemotherapy. By inhibiting the production of these proteins, dora might be softening that barrier, which could make cancer more vulnerable to treatment.

These molecules also produce signals that suppress the immune system, so when dora blocks them, it gives the immune system a fighting chance against the tumor.

They’re also involved in relaying growth signals to the tumor, which dora inhibits.

Gujral’s team discovered that dora is most effective when paired with other therapies in mice and human tumors.

“We found that in our 3D model, dora actually does work somewhat as a single agent,” Gujral said. “But later on in the paper we show that if you combine dora together with chemotherapy and [immunotherapy](#), it works great.”

The combination was particularly effective against breast and pancreatic cancers.

“We definitely saw a suppression in the tumor growth,” said Fred Hutch senior staff scientist Marina Chan, PhD, also a co-first author of the study.

The study opens many possibilities for further research, including a better understanding of what happens in the TME that diminishes the effectiveness of drugs that work well on isolated cancer cells in a dish.

The team is now applying this approach to screen for FDA-approved drugs in rare and challenging tumors directly from patients, providing a path to identify effective therapies where conventional approaches have often failed.

This work was supported by funding from the National Cancer Institute, a Cancer Center Support Grant, and the Breast Cancer Research Foundation (BCRF-17-035). Nao Nishida-Aoki is supported

by a Fred Hutch Interdisciplinary Training Grant Dual Mentor Fellowship in Cancer Research and JSPS overseas research fellowship. This research also was supported by the Comparative Medicine, Cellular Imaging, and Experimental Histopathology Shared Resource of the Fred Hutch/University of Washington Cancer/Seattle Children's Cancer Consortium.

John Higgins, a staff writer at Fred Hutch Cancer Center, was an education reporter at The Seattle Times and the Akron Beacon Journal. He was a Knight Science Journalism Fellow at MIT, where he studied the emerging science of teaching. Reach him at jhiggin2@fredhutch.org or [@jhigginswriter.bsky.social](https://bsky.app/profile/jhigginswriter.bsky.social).

[This article](#) was originally published September 24, 2025, by Fred Hutch News Service. It is republished with permission.

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