Medical Xpress

Improving breast cancer chemo by testing patient's tumors in a dish

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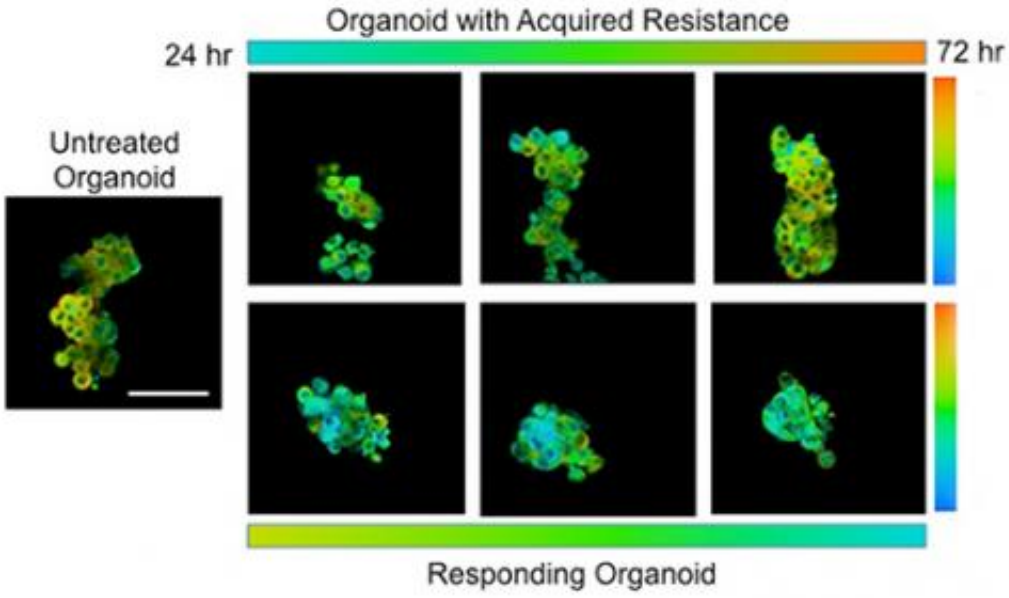


Time sequence shows the difference in response of organoids formed of drug-resistant cancer cells, top, and non-resistant cancer cells, bottom. Blue shades indicate that cell metabolism levels are low while yellow and orange indicate higher metabolic levels. Credit: Skala Lab, Vanderbilt University

One of the tragic realities of cancer is that the drugs used to treat it are highly toxic and their effectiveness varies unpredictably from patient to patient. However, a new "tumor-in-a-dish" technology is poised to change this reality by rapidly assessing how effective specific anti-cancer cocktails will be on an individual's cancer before chemotherapy

begins.

A team of biomedical engineers at Vanderbilt University headed by Assistant Professor Melissa Skala has developed the technique, which uses fluorescence imaging to monitor the response of three-dimensional chunks of tumors removed from patients and exposed to different anti-cancer drugs.

In an article published last month by the journal Cancer Research the engineers describe applying the technique to the three major forms of breast cancer. They report that the test can detect significant drops in the metabolic activity levels of all three types of tumors within 72 hours when exposed to an effective drug whereas tumors that were resistant to a drug show no change.

One in eight women in the United States will develop invasive breast cancer in their lifetime. Breast cancer kills about 40,000 women annually making it the second leading cause of cancer death in women – exceeded only by lung cancer, according to the American Cancer Society.

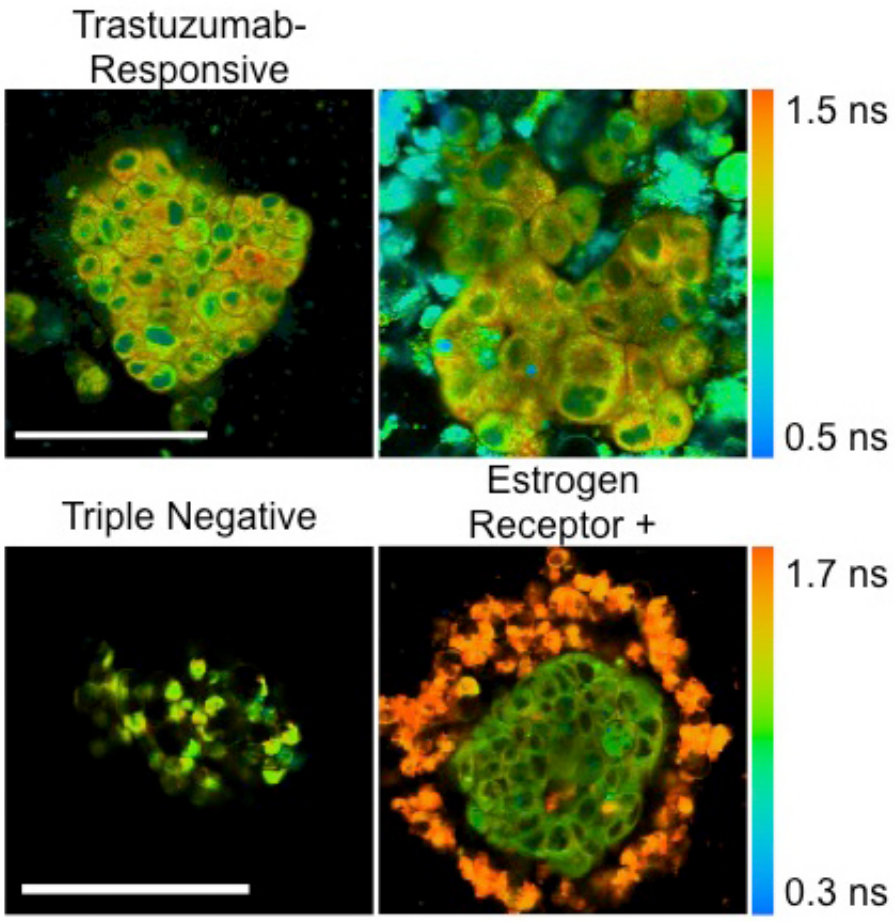
When breast cancer is diagnosed, the drug regimen that the patient receives is based primarily on the results of a biopsy that is used to identify the type of tumor she has. The effectiveness of the initial treatment is assessed after two to three months by determining whether the tumors are shrinking or continuing to grow.

According to several studies, in more than 100,000 cases each year the breast cancers never respond to the standard drugs, either initially or after repeated doses. As a result, 33 to 43 percent of patients must be switched to different drug combinations.

"Right now it's a guessing game," said Skala. "We hope that our test will

significantly improve the odds of survival of breast cancer patients by allowing doctors to identify the most effective but least toxic form of chemotherapy for each individual patient before the treatment begins."

More than 100 different anticancer drugs are currently available, but only 10 to 15 are used regularly.



Fluorescent images of breast tumor organoids show the level of metabolic activity in the pathways that the cells use to get the energy they need to divide. The blue color indicates a low activity level while orange represents a high activity level. The top two images are organoids of mouse breast tumor cells treated with the anticancer drug trastuzumab. The fact that they are predominantly blue indicates that the drug is inhibiting their growth.The bottom

two images are organoids made of two different types of human breast tumor cells: triple negative on the left and an estrogen receptor on the right. Credit: Skala Lab / Vanderbilt

The new "tumor in a dish" method begins by taking the cancerous tissue removed during surgery or biopsy, cutting it up into small pieces and putting them in a special collagen gel that maintains them as "organoids" that retain the three-dimensional structure of the original tumor and include supporting cells from the tumor's environment.

The traditional method of culturing tumor cells produces a single layer of cells that behave much differently from the original tumor. So cancer researchers have developed methods for culturing three-dimensional tumor organoids that mimic the behavior of the original tumors so they can study how they grow.

"This is the first time the 3-D culturing method has been used to predict the effectiveness of different drugs on tumors from individual patients," said graduate student Alex Walsh, who has played a key role in developing the test.

The researchers use a technique called "optical metabolic imaging" to measure the activity level of the organoids. The technique uses a laser that is tuned to the frequencies that cause two key enzymes in the cells to fluoresce. Measuring the variations in the intensity of the resulting fluorescence provides a "dynamic readout of cellular metabolism," which is a sensitive biomarker of drug response. Their tests show responses to drug exposures within 24 hours.

"We hit the tumor with a punch and see how it responds," said Skala, "It is cheap and fast and adaptable to high-throughput screening so it can be

used to test dozens of drugs or drug combinations at the same time."

The test also measures the responses of all the individual cells in the organoid. This is important because tumors are not all alike and some types of tumor cells may respond differently to a specific drug than another, Skala pointed out. If a given drug cocktail kills 90 percent of the cancer cells but doesn't affect the remaining 10 percent, the resistant tumor cells can take over and cause the tumor to grow back.

"Our test should make it possible to find drug combinations that kill ALL the cancerous cells in a tumor," Skala said.

So far they have tested the method extensively in mice and with six samples of human tumors using four anticancer drugs commonly used to treat breast cancer and two experimental drugs.

"The next step is to test tumors from more human patients and see how the results compare to the response that the patients have to chemotherapy," said Walsh.

If these experiments validate the test results, as the researchers expect, then they estimate that it could become available clinically within 5-10 years.

After validating the test for breast cancer, they intend to see how well it works with pancreatic cancer. Although pancreatic cancer is relatively rare, accounting for about 3 percent of all the cases of cancer in the United States, it has an extremely high mortality rate, so it accounts for about 7 percent of all cancer deaths.

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Vanderbilt University Medical Center along with Luigi Aurisicchio from Takis Biotech in Rome, Italy and Gennaro Ciliberto from the IRCCS National Cancer Institute in Naples, Italy also contributed to the research.

Provided by Vanderbilt University