**Combination Cancer Therapy Gives Cells a Knockout Punch**

[FEBRUARY 12, 2015](http://blog.cirm.ca.gov/2015/02/12/combination-cancer-therapy-gives-cells-a-knockout-punch/) / [ANNE HOLDEN](http://blog.cirm.ca.gov/author/aholdencirm/)

For some forms of cancer, there really is no way to truly eradicate it. Even the most advanced chemotherapy treatments leave behind some straggler cells that can fuel a relapse.

![By hitting breast cancer cells with a targeted therapeutic immediately after chemotherapy, researchers were able to target cancer cells during a transitional stage when they were most vulnerable. [Credit: Aaron Goldman] ]()By hitting breast cancer cells with a targeted therapeutic immediately after chemotherapy, researchers were able to target cancer cells during a transitional stage when they were most vulnerable. [Credit: Aaron Goldman]

But now, scientists have devised a unique strategy, something they are calling a ‘one-two punch’ that can more effectively wipe out dangerous tumors, and lower the risk of them ever returning for a round two.

Reporting in the latest issue of the journal [*Nature Communications*](http://www.nature.com/ncomms/2015/150211/ncomms7139/full/ncomms7139.html), bioengineers at Brigham and Women’s Hospital (BWH) in Boston describe how treating breast cancer cells with a targeted drug immediately after chemotherapy was effective at killing the cancer cells and preventing a recurrence. According to lead scientist Shiladitya Sengupta, these findings were wholly [unexpected](http://www.eurekalert.org/pub_releases/2015-02/bawh-opc021015.php):

In recent years, many scientists have suggested cancer stem cells are one of the biggest hurdles to curing cancer. [Cancer stem cells](https://www.cirm.ca.gov/our-progress/stem-cell-definitions#5) are proposed to be a subpopulation of cancer cells that are resistant to chemotherapy. As a result, they can propagate the cancer after treatment, leading to a relapse.

In this work, Sengupta and his colleagues treated breast cancer cells with chemotherapy. And here is where things started getting interesting.

After chemotherapy, the breast cancer cells began to morph into cells that bore a close resemblance to cancer stem cells. For a brief period of time after treatment, these cells were neither fully cancer cells, nor fully stem cells. They were in transition.

The team then realized that because these cells were in transition, they may be more vulnerable to attack. Testing this hypothesis in mouse models of breast cancer, the team first zapped the tumors with chemotherapy. And, once the cells began to morph, they then blasted them with a different type of drug. The tumors never grew back, and the mice survived.

Interestingly, the team did not have similar success when they altered the timing of when they administered the therapy. Treating the mice with both types of drugs simultaneously didn’t have the same effect. Neither did increasing the time between treatments. In order to successfully treat the tumor they had a very slim window of opportunity.

“By treating with chemotherapy, we’re driving cells through a transition state and creating vulnerabilities,” said Aaron Goldman, the study’s first author. “This opens up the door: we can then try out different combinations and regimens to find the most effective way to kill the cells and inhibit tumor growth.”

In order to test these combinations, the researchers developed an ‘explant,’ a mini-tumor derived from a patient’s biopsy that can be grown in an environment that closely mimics its natural surroundings. The ultimate goal, says Goldman, is to map the precise order and timing of this treatment regimen in order to move toward clinical trials.

One-two punch catches cancer cells in vulnerable state

*Transition state may offer important window of time for treatment*

BRIGHAM AND WOMEN'S HOSPITAL

Timing may be decisive when it comes to overcoming cancer's ability to evade treatment. By hitting breast cancer cells with a targeted therapeutic immediately after chemotherapy, researchers from Brigham and Women's Hospital (BWH) were able to target cancer cells during a transitional stage when they were most vulnerable, killing cells and shrinking tumors in the lab and in pre-clinical models. The team reports its findings in Nature Communications on February 11.

"We were studying the fundamentals of how resistance develops and looking to understand what drives relapse. What we found is a new paradigm for thinking about chemotherapy," said senior author Shiladitya Sengupta, PhD, associate bioengineer at BWH.

Previous studies have examined cancer stem cells (CSCs) - small populations of cells within a tumor that are resistant to chemotherapy. Sengupta and his colleagues took breast cancer cells that did not have the markings of CSCs and exposed them to docetaxel, a common chemotherapy drug. The team found that after exposure to chemotherapy, the cells began developing physical markings usually seen in CSCs, including receptors on the cell surface to which specific proteins can bind. These "markers of stemness" suggested that the cells were transitioning into a different state, during which time they might be vulnerable to other cancer drugs.

To test this, the researchers treated the cells with a variety of targeted therapeutics immediately after chemotherapy. The researchers observed that two drugs each killed a large fraction of the cells that had begun transitioning: dasatinib, a drug that targets the Src Family Kinase (SFK) and RK20449, a new drug in pre-clinical testing that specifically targets one of the SFK proteins called Hck. The researchers confirmed these findings in a mammary carcinoma mouse model - treatment with dasatinib just a few days after administering two high doses of chemotherapy prevented tumor growth and increased survival rates. Treating cells simultaneously with docetaxal and dasatinib or administering dasatinib after a longer period of time did not produce the same effects. The researchers theorize that the cancer cells go through a temporary transition state, which means that administering the drugs in a very specific timeframe and sequence is important.

"By treating with chemotherapy, we're driving cells through a transition state and creating vulnerabilities," said first author Aaron Goldman, PhD, a postdoctoral fellow in biomedical engineering at BWH. "This opens up the door: we can then try out different combinations and regimens to find the most effective way to kill the cells and inhibit tumor growth."

To make these observations, the researchers developed and leveraged three-dimensional "explants" - tissue derived from a patient's tumor biopsy and grown in serum from that specific patient for research purposes. This model mimics the tumor's microenvironment and preserves the tumor's cellular diversity.

In a continuation of this work, Goldman is also using mathematical modeling to pursue the most effective dose of chemotherapy to induce the vulnerable transition state of the cancer cell demonstrated in this research.

"Our goal is to build a regimen that will be efficacious for clinical trials," said Goldman. "Once we understand specific timing, sequence of drug delivery and dosage better, it will be easier to translate these findings clinically."

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