

Researchers Learn How a Drug Called Zotatfin Kills Cancer Cells

Zotatifin, developed by UCSF researchers, is being tested against breast cancer. It also might work against prostate and other cancers.

April 7, 2025 By University of California San Francisco and Levi Gadye

Swirling inside every cell are millions of microscopic messages called messenger RNAs (mRNAs). The messages are the genetic blueprints for proteins, which determine the behavior and health of the cell.

All mRNAs are packaged to ensure they're only used at the right place and time — imagine notes sealed in envelopes. But in cancer, enzymes called helicases relentlessly unseal thousands of mRNAs, leading to out-of-control protein production.

Now, University of California, San Francisco scientists have discovered that a cancer drug called zotatifin that they helped invent turns this process on its head. It disables a helicase called eIF4a, which is plentiful in all sorts of tumors. The drug not only stopped prostate tumors from growing in mice but also made them shrink.

The study, which was funded by the National Institutes of Health (NIH), the Prostate Cancer Foundation (PCF), the UCSF Benioff initiative for prostate cancer research, and individual donors, appears in [Cancer Cell](#) on March 20.

“Healthy cells have all sorts of safeguards to prevent cancerous mRNAs from being highly translated,” said [Davide Ruggero](#), PhD, a professor of urology at UCSF, Goldberg-Benioff Endowed Professorship, American Cancer Society Research Professor and co-corresponding author of the paper. “Prostate cancer usurps eIF4A to overcome these safeguards, but we had zotatifin in our back pocket to attack eIF4A. We think it could be a game-changer for treating the disease.”

Targeting the protein factories behind prostate cancer

Zotatifin was developed by the pharmaceutical company eFFECTOR based on the research of Ruggero and [Kevan Shokat](#), PhD, professor of cellular and molecular pharmacology at UCSF. It is currently being tested as a therapy for breast cancer in clinical trials.

Ruggero and his UCSF team suspected that eIF4A might also be misbehaving in prostate cancer, so they screened tumors from 500 UCSF patients with prostate cancer. As the patients' cancer worsened, their eIF4A levels rose.

The scientists tested zotatifin against prostate tumor biopsies that were transplanted into mice. This type of experiment, called a patient-derived xenograft, is considered a gold standard for showing a drug's potential to beat cancer in the laboratory.

The prostate tumors, which had been growing relentlessly in patients, shrank in response to zotatifin in the mice.

Ruggero knew that this first result might not be enough to show it worked against prostate cancer, which is one of the most common cancers in men. It is notorious for coming back after diminishing in response to first-line therapies, like hormone therapy and radiation.

The scientists measured the types and amounts of proteins present in prostate cancer cells before and after zotatifin. With zotatifin interfering with eIF4A, it lowered the amount of specific proteins that drive cancer. One of them was the androgen receptor, which is a major driver of prostate cancer. Several prostate cancer therapies try to block the receptor, but zotatifin prevented cancer cells from even making it.

When eIF4A tried to unpackage the androgen receptor mRNA in the presence of zotatifin, it got tangled up in the mRNA. The tangled message couldn't fit into the cell's machinery for making a protein and failed to make any more of the androgen receptor.

The same was true for the mRNA that makes HIF1A, an enzyme that helps prostate tumors grow in the absence of oxygen.

"Zotatifin, as a bona-fide 'translatome therapy' that blocks the production of cancer-causing proteins, expands the landscape of drugs available for patients," said [Duygu Kuzuoglu-Ozturk](#), PhD, a scientist in Ruggero's lab and co-first author of the paper.

The team hopes their results will encourage clinical trials of zotatifin against prostate cancer.

"Our innovative approach with zotatifin promises to make prostate cancer treatment more durable," said [Hao Nguyen](#), MD, PhD, professor of urology at UCSF and co-first and co-corresponding author of the paper. "It offers much-needed hope for the tens of thousands of patients battling this deadly disease."

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