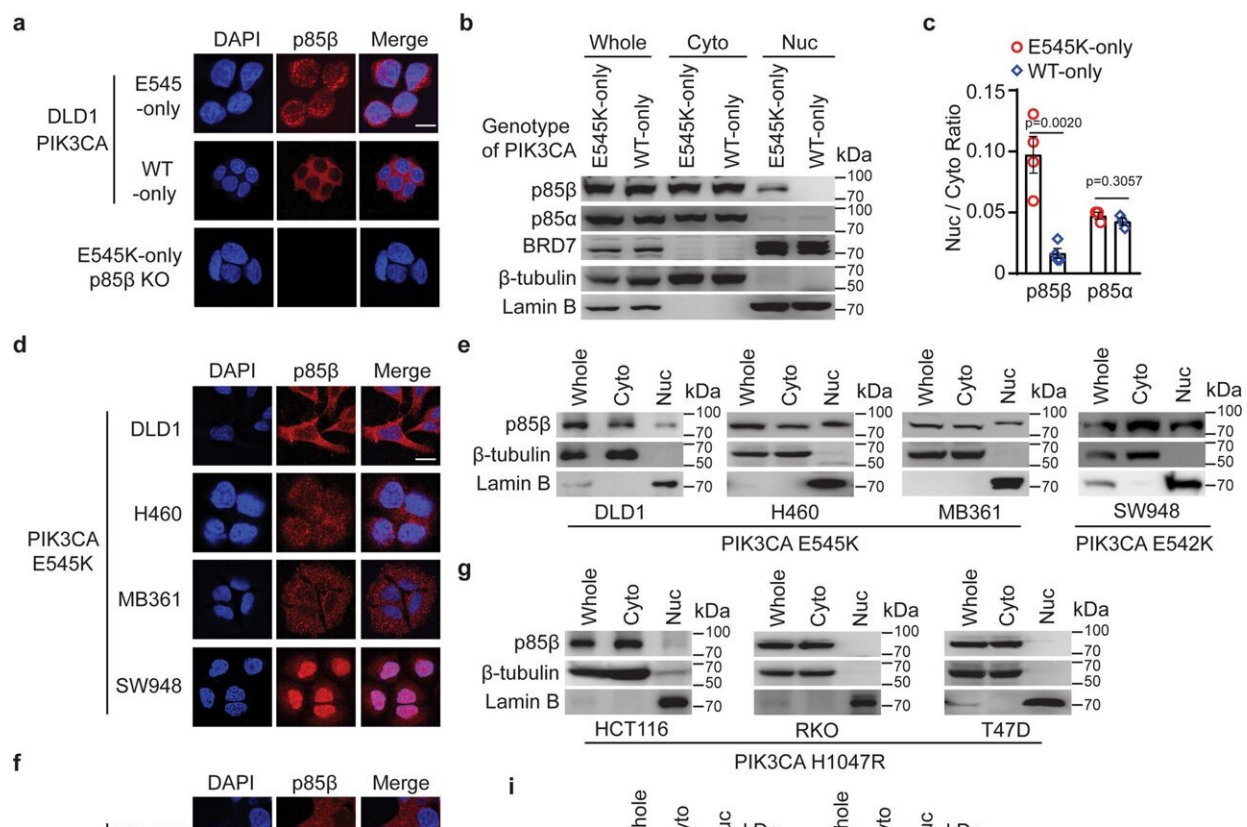


New research supports combining two clinical cancer drugs to treat specific colorectal cancers

May 2 2022



p85β translocates into the nucleus in cancer cells with a PIK3CA E545K mutation. a–c p85β translocates into the nucleus in DLD1 PIK3CA E545K cells. a The indicated cells were immunofluorescently stained with an anti-p85β antibody and DAPI. b Cell lysates were fractionated into cytoplasmic (Cyto) and nuclear (Nuc) fractions and blotted with the indicated antibodies. Whole: whole cell lysate. The ratios of nuclear/cytoplasmic p85β levels were quantified by

Image J as shown in (c). Data are presented as mean \pm SEM of three (p85 α) or four (p85 β) independent experiments. d–j p85 β translocates into the nucleus in cancer cells with a PIK3CA helical domain mutation, but not cells with WT PIK3CA or a PIK3CA kinase domain mutation. The indicated cells were immunofluorescently stained with an anti-p85 β antibody and representative images are shown in (d), (f), and (h). Cell lysates of the indicated cells were fractionated into cytoplasmic and nuclear fractions and blotted with the indicated antibodies (e), (g), and (i). The ratios of nuclear/cytoplasmic p85 β levels were quantified by Image J and shown in (j). Data are presented as mean \pm SEM of three independent experiments. The student's t-test (two-tailed) was used for statistical analyses. Source data are provided as a Source Data file. Scale bars = 10 μ m. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-29585-x

Researchers at the Case Western Reserve University School Medicine have found that combining two cancer drugs can be effective in treating a specific type of colorectal cancer, according to a new study published in *Nature Communications*.

Their study focuses on a [colon cancer](#) involving a mutation in a specific part of the PIK3CA gene, known to account for about 25,000 colorectal cancer patients—or about 15% of colorectal cancers—each year in the United States.

The Case Western Reserve-led team found evidence that combining the drugs Apellisib and Tazemostat to target the two signaling pathways involving these mutations was effective.

Based on their findings, [clinical trials](#) using the drug combination to treat this type of colorectal cancer are expected to begin on [human patients](#) later this year.

"Ultimately, the efficacy of the drug combination needs to be tested in [cancer patients](#)," said Zhenghe Wang, the Dale H. Cowan M.D.—Ruth Goodman Blum Professor of Cancer Research at the School of Medicine. "We are actively pursuing phase 1 clinical trials in patients whose tumors have this genetic mutation and the clinical trials are led by Dr. David Bajor, an oncologist, at University Hospitals."

Tazemostat is a clinical drug approved by the U.S. Food and Drug Administration (FDA) to treat a type of blood cancer. The drug Apolisib, meanwhile, is FDA-approved to treat some breast cancers.

Colorectal cancer is the second-leading cause of cancer-related deaths, and as many as 151,000 new cases of colorectal cancer will be diagnosed in 2022, according to the National Cancer Institute.

Understanding the PIK3CA tumor mutation

The development of cancer cells is driven by oncogenes, which, when mutated, act as a gas pedal to accelerate growth. Conversely, tumor suppresser genes act as a brake to slow down cancer cell growth.

Some types of hard-to-treat colorectal cancer tumors contain a mutation in the oncogene PIK3CA, which is an abbreviation for the scientific name for gene coding called "p110 α of phosphatidylinositol 3-kinase" (PI3K). Researchers say that PIK3CA is mutated in about 30% of [colorectal cancers](#) and in 20% of all human cancers.

Wang, the principal investigator on this study, co-discovered the PIK3CA mutation in 2004.

"The PIK3CA mutation is found in up to 40 tumor types and affects an estimated 4 million patients each year worldwide," Wang said. "There is no targeted treatment for PIK3CA mutant [colorectal cancer](#), and our

research may lead to new therapy options."

The scientists wanted to target the PIK3CA mutations that occur in what's referred to as the "helical domain," which, according to Wang, is a hotspot for mutations. The team hypothesized that the PIK3CA mutation in the helical domain and its two related pathways could hold the solution.

"The PIK3CA cancer cell mutation has two different pathways, and both must be inhibited chemically, which is where the two-drug combination therapy comes into play," Wang said.

By studying colorectal tumor cells in research models, the scientists were able to determine a two-pronged drug treatment option involving Tazemostat and Apelisib would be most effective.

Data showed that the cancer tumor continued growing in mouse models when treated with only one drug, but shrank when treated with the dual [drug combination](#).

More information: Yujun Hao et al, Nuclear translocation of p85 β promotes tumorigenesis of PIK3CA helical domain mutant cancer, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-29585-x](https://doi.org/10.1038/s41467-022-29585-x)

Provided by Case Western Reserve University

Citation: New research supports combining two clinical cancer drugs to treat specific colorectal cancers (2022, May 2) retrieved 4 July 2023 from <https://medicalxpress.com/news/2022-05-combining-clinical-cancer-drugs-specific.html>

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