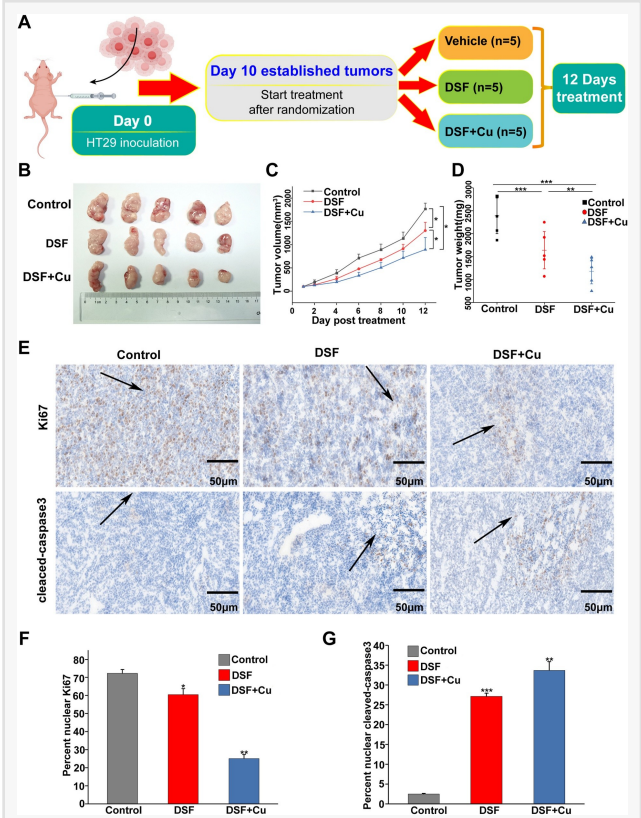
Metabolic Enzyme Identified as a Selective Vulnerability in APC-Deficient Cancer Cells

SHANNON, CLARE, IRELAND, April 7, 2026 /EINPresswire.com/ -- A precision cancer strategy that selectively kills tumour cells while leaving healthy tissue intact may be within reach for the majority of colorectal cancer patients, according to new research published in Genes & Disease. The study identifies a previously unexplored synthetic lethal interaction between two genes — adenomatous polyposis coli (APC) and aldehyde dehydrogenase 2 (ALDH2) — offering a genetically targeted treatment strategy built around one of the most common mutations in the disease.



Validation of ALDH2 as a synthetic lethal partner of APC using xenograft tumor models

Colorectal cancer (CRC) is the fourth leading cause of cancer death globally, and the APC tumour suppressor gene is mutated in more than 60% of cases, making it one of the most prevalent genetic drivers of the disease. Despite its frequency, APC has proven exceptionally difficult to target directly. The research team, led by scientists at Nanjing Normal University, took a different approach: rather than targeting APC itself, they searched for a partner gene whose inhibition would be catastrophic only in cells that had already lost APC function — leaving normal cells unharmed.

Using bioinformatics screening across multiple synthetic lethality databases, the team identified ALDH2, a mitochondrial enzyme that helps neutralise toxic aldehydes and clear reactive oxygen species (ROS) — chemically unstable molecules that, in excess, trigger cell death. Their central insight was that APC-deficient cancer cells already operate under elevated oxidative stress, producing abnormally high ROS levels and sitting perilously close to a toxic threshold.

When the team inhibited ALDH2 using disulfiram, a compound that blocks the enzyme's detoxifying activity, that threshold was crossed. ROS levels in APC-deficient cells surged past a breaking point, activating a cascade through the ROS/ASK1/JNK signalling pathway that ended in

programmed cell death. Critically, CRC cells with intact APC showed no equivalent vulnerability — their ALDH2 continued managing oxidative stress effectively, and the treatment left them largely unaffected.

The effect held across multiple experimental systems. In laboratory cell lines, APC-deficient tumour cells showed dramatically reduced proliferation, G0/G1 cell cycle arrest, and a sharp increase in apoptosis following treatment, with activation of pro-death proteins including BAX, cleaved caspase-3, and PARP1. When copper ions were added alongside disulfiram — a combination known to amplify the compound's enzymatic inhibition — the effect was stronger still. In live animal models, this combination substantially reduced both tumour volume and weight compared to untreated controls, while showing no significant therapeutic effect on tumours carrying wild-type APC, confirming the genotype-specific selectivity of the approach.

The findings reposition disulfiram as a potential precision oncology agent, one whose deployment would be guided directly by a patient's mutational profile. Because APC status is already routinely assessed in CRC diagnosis, identifying eligible patients would require no new screening infrastructure. The authors stress, however, that rigorous clinical trials remain essential, noting important differences between animal models and human pharmacology that must be resolved before the strategy can reach patients.

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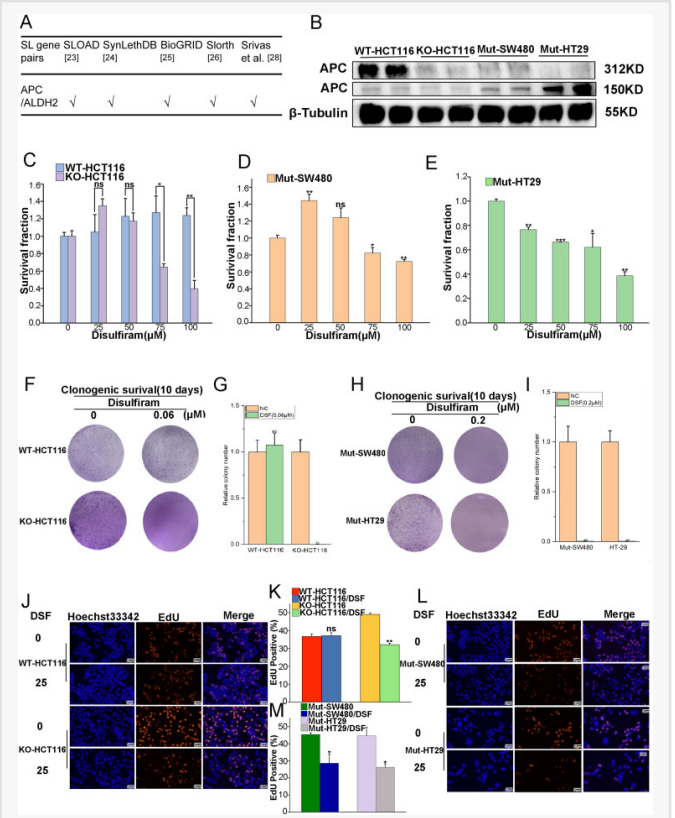
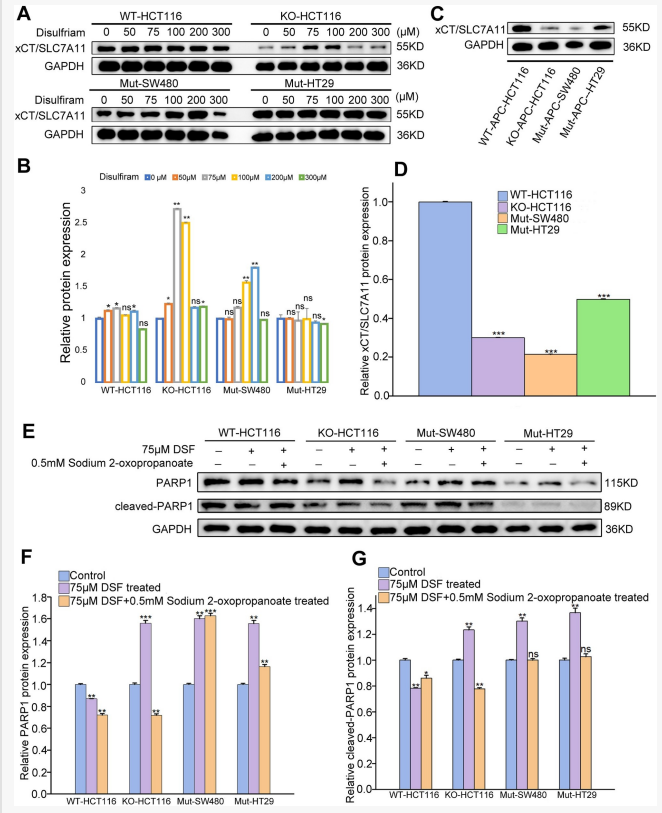


Synthetic lethality in APC-deficient CRC cell lines treated with ALDH2 inhibitors.



Activation of the ROS/ASK1/JNK pathway induces apoptosis in APC-deficient CRC cell lines treated with an ALDH2 inhibitor.

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