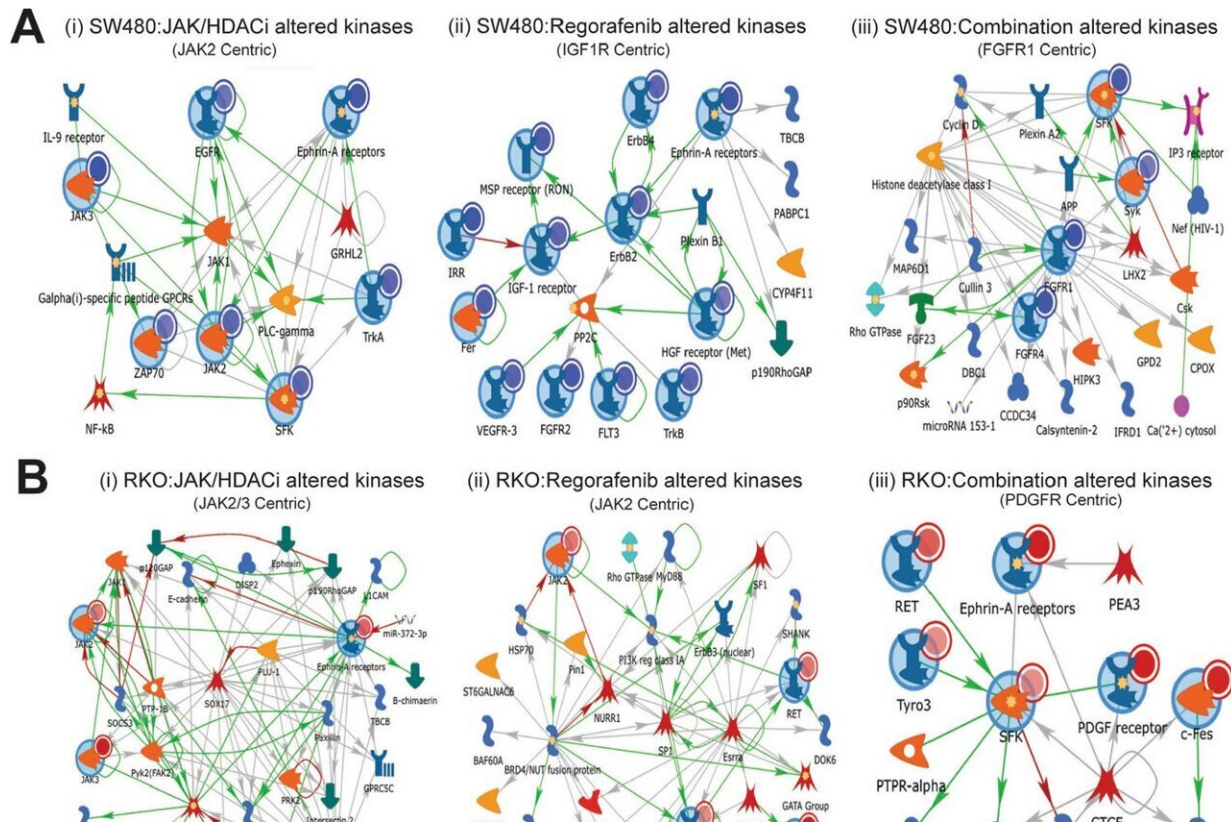


# New combination therapy may offer a safer, more effective treatment for colorectal cancer

September 4 2024, by Adam Pope



Combination treatment of JAK/HDACi and regorafenib decreases kinase activity in CRC cells. Credit: *Journal of Experimental & Clinical Cancer Research* (2024). DOI: 10.1186/s13046-024-03106-8

Researchers from the University of Alabama at Birmingham have identified a promising new combination therapy for metastatic colorectal

cancer that enhances the effectiveness of existing treatment while reducing harmful side effects.

The [study](#), published in the *Journal of Experimental & Cancer Research*, focused on regorafenib, a drug that modestly improves survival in mCRC patients but often leads to severe toxicities. By pairing regorafenib with a dual JAK/HDAC inhibitor at low doses, the researchers were able to significantly boost the drug's anticancer activity.

Colorectal cancer is a leading cause of cancer-related deaths worldwide. For patients with metastatic disease, [treatment options](#) are limited and the prognosis is often poor. Regorafenib, a multiple-kinase inhibitor, is one of the few drugs available for these patients; but its use is hampered by significant toxicity, limiting its clinical benefit.

The research team, led by UAB Department of Pathology Professor Upendar Manne, Ph.D., conducted a series of experiments using colorectal cancer cell lines, patient-derived xenografts and mouse models to test the efficacy of the [combination therapy](#).

They examined the effects of the combination on cell viability, cell cycle progression, apoptosis (programmed cell death) and molecular signaling pathways. Researchers explored how the treatment influenced the [immune response](#) to the tumors.

"Findings of our study have opened new hope for translating this breakthrough into a widely accessible treatment for metastatic colorectal cancer," Manne said. "For our team, this is a continuation of our quest to outsmart cancer, one discovery at a time."

The combination therapy outperformed regorafenib alone across several metrics. It significantly reduced tumor cell viability, induced cell cycle arrest at the G0-G1 phase and promoted apoptosis. The combination also

inhibited key molecular pathways involved in cancer growth, including those regulated by JAKs, STAT3 and EGFR. Importantly, the treatment enhanced the immune system's ability to target the tumor, as evidenced by increased infiltration of immune cells in the tumor microenvironment.

In animal models, the combination therapy led to a significant reduction in tumor growth and metastasis. Pharmacokinetic studies further revealed that the combination increased the bioavailability of regorafenib, meaning more of the drug was available to exert its effects, potentially allowing for lower doses and reducing toxicity.

The study's findings suggest that combining regorafenib with a dual JAK/HDAC inhibitor could be a more effective and safer approach to treating [metastatic colorectal cancer](#). The promising preclinical results pave the way for [clinical trials](#) to evaluate the potential of this combination therapy in patients. If successful, this approach could provide a new lifeline for those battling advanced colorectal cancer, offering hope for improved outcomes with fewer side effects.

**More information:** Prachi Bajpai et al, Combination of dual JAK/HDAC inhibitor with regorafenib synergistically reduces tumor growth, metastasis, and regorafenib-induced toxicity in colorectal cancer, *Journal of Experimental & Clinical Cancer Research* (2024). [DOI: 10.1186/s13046-024-03106-8](https://doi.org/10.1186/s13046-024-03106-8)

Provided by University of Alabama at Birmingham

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