One-two punch of drugs better than either alone against colorectal cancer

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Drugs PF-04691502 and PD-0325901 are greater against colorectal cancer than the sum of their parts.

Genes make proteins and proteins tell your body's cells what to do: one talks to the next, which talks to the next, and to the next. Like a game of telephone, researchers call these "signaling pathways". Abnormalities in these signaling pathways can cause the growth and survival of cancer cells. Commonly, mutations or rearrangements of genes in the MAPK

signaling pathway create cancer's fast growth, and alterations in the PI3K signaling pathway allow cancer cells to survive into virtual immortality.

Of course, researchers have extensively targeted these two signaling pathways, designing drugs that turn on or off genes in these pathways, thus interrupting the transmission of cancer-causing signals. Unfortunately, these pathways have proven difficult to drug and also it has been difficult to show the effectiveness of drugs that successfully interrupt the transmission of signals along these pathways.

A study by the University of Colorado Cancer Center published in the journal *PLoS ONE* and concurrent phase I clinical trial is examining a new strategy: targeting both these important cancer-causing pathways simultaneously.

"Well, these two pathways are mutated frequently in cancer. Why not hit both of them? It was as simplistic as that," says Todd Pitts, MS, research instructor in the Program for the Evaluation of Targeted Therapies, and the study's first author.

The study used colorectal cancer tumors grown on mice from samples of patient tumors, called "patient-derived xenograft" models. To these tumors, Pitts and colleagues added the experimental anti-cancer drugs PF-04691502 and PD-0325901, the first of which mutes a link in the PI3K signaling pathway and the second of which mutes a link in the MAPK signaling pathway. In this case, the combination was greater than the sum of the parts - alone, PF-04691502 and PD-0325901 modestly inhibit the growth and survival of colorectal cancer in these models; after 30-day exposure to the combination, colorectal cancer cells were killed much more effectively than by either drug alone, and even more effectively than if you added together the cells killed by each drug alone.

"There was also a huge variation in how effectively cells were killed in

some models compared to others," Pitts says. Continuing lab work seeks to discover ways to predict which tumors will respond to the drug combination and which may be better treated by other means.

While Pitts is working with colorectal cancer tumors grown in the lab, the same combination of drugs is being tested in a multi-site phase I clinical trial (Clinicaltrials.gov #NCT01347866). Steve Leong, MD, is the principal investigator at the CU Cancer Center site, with additional U.S. sites including the Hollings Cancer Center in South Carolina and the UCLA Medical Center in California.

"This study demonstrates strong potential for this combination in treating laboratory models of colorectal cancer. We hope that if we can discover biomarkers that predict which tumors respond and which don't respond to the combination that we can optimize its use. And in the meantime, Dr. Leong and colleagues have the combination in the clinic where we hope to see its benefit with patients," Pitts says.

More information: *PLoS ONE* , www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0113037

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