

Researchers uncover a viable way for colorectal cancer patients to overcome drug resistance

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When combined with other treatments, the drug cetuximab—which works by slowing or stopping the growth of cancer cells—has been shown to extend survival in certain types of cancer, including metastatic colorectal cancers. Unfortunately, about 40 percent of colorectal cancer patients—specifically those who carry a mutated form of a gene called KRAS—do not respond to the drug. Researchers at Fox Chase Cancer Center in Philadelphia, however, have been working on a way to overcome this resistance to cetuximab by unleashing a second cetuximab driven mechanism using a novel drug called ARI-4175. The researchers from Fox Chase will present their findings at the AACR Annual Meeting 2012 on Wednesday, April 4.

In mice that had KRAS mutated colorectal cancer, researchers found that ARI-4175 not only blocked tumor growth when used alone, but also when used in combination with cetuximab. They hypothesize that the new drug may work by enlisting "natural killer" cells of the body's own immune system to reject the tumor.

"We've discovered that ARI-4175 appears to increase the level of natural killer cells that could play a role in rejecting the tumor," Hossein Borghaei, D.O., director of thoracic medical oncology at Fox Chase and lead author on the study says. He notes that this action—rallying the body's own immunologic defenses—may explain why ARI-4175 effectively stops the growth of tumors. "My theory is that this particular

drug turns on the host's anticancer immune response, while cetuximab serves to help direct it toward the cancer."

Borghaei, along William W. Bachovchin, Ph.D., professor of biochemistry at Tufts Sackler School of Graduate Biomedical Sciences (also co-author on the study) and colleagues, tested ARI-4175 in colorectal cancer cell lines and in mice with two types of cetuximab-resistant colorectal tumors. Neither cetuximab nor ARI-4175, separately or together, succeeded in killing the cells in lab dishes. In the mice, however, ARI-4175 blocked tumor growth, and was more successful at higher doses of the drug. The research shows an even stronger effect in mice that received ARI-4175 combined with cetuximab.

Cetuximab, which is FDA-approved for metastatic colorectal cancer and some head and neck cancers, works by blocking a crucial receptor on the surface of a cancer cell—causing the cell to die. In people carrying the mutated form of the KRAS gene, cetuximab is not effective, but ARI-4175 may open up a detour around that impasse.

Borghaei notes that a cancer treatment like the immune stimulator ARI-4175, which uses the body's own defenses, may be more effective than drugs targeting tumor oncogenes that are susceptible to mutations that lead to resistance. "Tumors often develop resistance to targeted therapies," he says, "but it's more difficult to find resistance to a patient's own immune system. Bringing in the activity of the immune system might be the most effective way to fight some of these cancers."

"Our immune system can actually be a very useful partner in the fight against cancer," he says.

The researchers say their results suggest ARI-4175 warrants further testing in clinical trials. Although the researchers investigated [colorectal cancer](#), their findings may also point to new approaches to treating other

types of cancer. "If we can show that the drug overcomes resistance to cetuximab, it can be used against head and neck cancers as well," says Borghaei.

Provided by Fox Chase Cancer Center

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