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Dual Drug Treatment Prevents Formation of Colon Tumors in Mice

By combining an aspirin-like compound with a drug that inhibits epidermal growth factor activity, scientists have nearly eliminated pre-cancerous colon polyps in mice that are susceptible to developing colon tumors.

If the drug combination strategy makes its way through further animal testing and then through human clinical trials, it could become a powerful preventive therapy for human colon cancer, the second leading cause of cancer deaths in the United States. Currently, more than half of the Western population develops intestinal polyps, and about ten percent of these cases will progress to malignancy.

Howard Hughes Medical Institute (HHMI) investigator Bert Vogelstein, HHMI associate Christopher Torrance and their colleagues at The Johns Hopkins University Oncology Center and Wyeth-Ayerst Research reported that combination therapy of the drugs sulindac and EKB-569 successfully blocked the development of pre-cancerous polyps in mice. The mice possess a genetic defect similar to that found in humans with familial adenomatous polyposis (FAP), a syndrome that confers susceptibility to colon cancer. The researchers published their findings in the September 2000 issue of *Nature Medicine*.

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Sulindac is a non-steroidal anti-inflammatory drug (NSAID) that has long been used to help prevent the development of intestinal polyps that can lead to colon cancer. Unfortunately, NSAID use in prevention of colon cancer has been limited because chronic administration of NSAIDs can lead to significant toxicity for patients. EKB-569 is a new drug developed at Wyeth-Ayerst Research that inhibits the activity of the epidermal growth factor (EGF) receptor, which is known to be involved in the development of

colon tumors.

The scientists found that the combination of sulindac and EKB-569 achieved a better than 95 percent reduction in the number of cancerous polyps. In contrast, 100 percent of a control group of the mice that did not receive the drugs developed multiple tumors.

"The most surprising thing was that about half the treated mice got absolutely no tumors at all, which was quite unprecedented," said Vogelstein. "And even the animals that did get tumors only had one or two, compared to the untreated control mice which developed an average of 20 tumors. So, we felt very encouraged by these results."

Particularly important, said Vogelstein, is that the use of EKB-569 allowed the scientists to trim the effective dosage of sulindac down to about one-quarter of the amount that produces protection when sulindac alone is administered.

Vogelstein emphasized that the new findings offer general lessons of the importance of research and development on preventive cancer treatments. The power of the dual drug treatment, said Vogelstein, lies in the fact that each drug inhibits a different metabolic signaling pathway important for the generation of malignant cells. While EKB-569 inhibits the EGF signaling pathway, sulindac inhibits cyclooxygenases (COX) and other proteins that stimulate cell proliferation, angiogenesis and other processes key to tumor formation.

"Preventive strategies in general have not been a target of nearly as much research as therapeutic strategies," Vogelstein said. "And the old adage 'an ounce of prevention is worth a pound of cure,' is definitely true for cancers."

Vogelstein said that extensive toxicity testing must be done in animals before clinical trials of the dual-drug therapy can begin in humans. He anticipated that such trials could begin in a year.

"We plan particularly rigorous toxicity trials in animals, because with chemoprevention approaches—when you're proposing to treat patients who are otherwise healthy—greater caution is necessary," said Vogelstein. Fortunately, he noted, sulindac has already been used clinically for years, and the combination with EKB-569 allows the dosage of sulindac to be lowered considerably.

In a *News & Views* article in the same issue of *Nature Medicine*, Rajnish Gupta and Raymond Dubois at Vanderbilt University Medical Center write: "The results of Torrance et al., may be a harbinger for the eventual development of effective combinatorial regimens for cancer prevention in humans, allowing optimism for the development of effective cancer prevention strategies."