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MECHANISMS AND APPLICATIONS OF NSAIDS IN THE CHEMOPREVENTION OF CANCER

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Significant evidence exists which demonstrates that inflammation predisposes and promotes the cancer process in humans. Chronic inflammation can induce cancer in a variety of organ sites, including bowel and lung. There is also firm evidence that induced cyclooxygenases and nitric oxide synthetases, prostaglandins, and inflammatory cytokines can promote and accelerate the carcinogenic process. For nearly a decade the National Cancer Institute has been developing nonsteroidal anti-inflammatory drugs (NSAIDs) for the purpose of preventing a variety of cancers. Preclinical data has shown that, as a chemical class, the NSAIDs were extremely effective in preventing carcinogen-induced cancers in a wide variety of organ sites, most notably colon, bladder and skin. Of the agents tested sulindac, piroxicam and celecoxib were the most potent inhibitors. Following an NCI sponsored Phase 2 clinical trial in 1999, the United States Food and Drug Administration approved celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, as an adjunct to usual care for patients with familial adenomatous polyposis. Additional NCI clinical trials are underway for the prevention of sporadic colon cancer, hereditary nonpolyposis colon cancer, Barretts esophagus, bladder dysplasia, and actinic keratoses. Increased expression of COX-2 mRNA was reported in 12 out of 14 (86%) human colon carcinoma samples and in 6 (43%) of 14 unpaired colon adenomas. Similar chemopreventive efficacy has been reported with other COX-2 inhibitors, including NS-398 and nimesulide in a rat colon cancer model. Selective inhibition of COX-2, the inducible form of COX, is a promising approach in the development of chemopreventive agents that are less toxic than drugs inhibiting both COX-1 and COX-2 isoenzymes.