

**P001** Influenced of polyamine depletion on NSAID-induced cytotoxicity in colorectal cancer cells

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Colorectal cancer is the third most common cancer with a current 5 year survival rate is around 40%. Thus an alternative strategy to current treatment is required. Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) decreases colorectal cancer incidence by up to 50%. The mechanism of action of NSAIDs pharmacologically is through cyclooxygenase (COX) inhibition but recent evidence suggests that in cancer cells cytotoxicity is via a COX-independent pathway. Polyamines are naturally occurring growth factors important in cell proliferation present in increased concentrations in human colorectal cancers. The metabolism of polyamines is regulated by the rate-limiting enzyme ornithine decarboxylase (ODC). ODC can be irreversibly inhibited by  $\alpha$ -difluoromethylornithine (DFMO), causing polyamine depletion and decreased cell growth. Depletion of polyamines by DFMO results in the attenuation of NSAID-induced cytotoxicity, which can be partially reversed through the readdition of exogenous polyamines. DFMO acts by direct inhibition of ODC but NSAIDs do not directly act on ODC. Therefore there may be competition between these drugs to inhibit ODC. NSAIDs may act indirectly on ODC through the induction of a specific protein inhibitor of ODC, antizyme, which targets ODC for degradation.