

P004 Molecular targets of nitric oxide-donating aspirin (NO-ASA) in cancer

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NO-ASA consisting of ASA plus an $-ONO_2$ moiety linked to it via a molecular spacer is a new drug for cancer prevention. NO-ASA seems to overcome the low potency and toxicity of traditional ASA. The $-ONO_2$ is responsible for releasing NO, and it appears to be required for biological activity. *In vitro* studies: NO-ASA inhibits the growth of colon, pancreatic, prostate, lung, skin, leukemia, and breast cancer cells, being up to 6,000-fold more potent than traditional ASA. This effect is due to: a) *Cell kinetics*: inhibition of proliferation (PCNA), induction of apoptosis (multiple criteria) and blocking the G1 to S cell cycle transition; and b) *Cell signaling*: inhibition of Wnt signaling ($IC_{50} = 0.2 \mu M$), inhibition of NF- κB activation ($IC_{50} = 7.5 \mu M$); inhibition of NOS2 expression ($IC_{50} = 48 \mu M$); inhibition of MAPK signaling ($IC_{50} = 10 \mu M$) and induction of COX-2 at $\sim 10 \mu M$. *In vivo* studies: NO-ASA inhibits intestinal carcinogenesis in Min mice (tumor multiplicity reduced by 59% after three weeks; no effect in control animals; no side effects) and in the *N*-nitrosobis(2-oxopropyl)amine model of pancreatic cancer 89% reduction in NO-ASA [3,000 ppm in the diet]-treated animals [$P < 0.001$]; no statistically significant effect by traditional ASA at equimolar doses. Our data indicate that NO-ASA is a highly promising agent for the prevention and/or treatment of cancer.