Oral Presentations

[OA-1] [10/18/2002 (Fri) 11:30 - 11:40 / Hall A]

Development of a new Cox-2 inhibitor as an anticancer agent

Park Jeong Ran°, Kang Jin Hyoung, Noh Ji Young[1], Ryu Hyung Chul[1], Park Sang Wook[1], Cho Il Hwan[1], Hwang Daniel H[2], Kim In Kyung, Kuh Hyo Jeog

Catholic Res Inst of Med Sci, Catholic Univ of Korea, Seoul, [1]Inst of Science & Technology, Cheil Jedang Corporation, Inchon, South Korea and [2]Pennington Biomedical Res Center, Louisiana State Univ., LA, CA

Cyclooxygenase (Cox-2) is involved in tumorigenesis, hence, considered to be a molecular target for chemoprevention and chemomodulation. Selective Cox-2 inhibitors including Celecoxib and Nimesulide have been studied for their anticancer activity when given alone and in combination with radiation or cytotoxic agents. In this study, we synthesized more than 140 analogues of Celecoxib and Nimesulide, and evaluated their inhibitory effects on Cox-1 and Cox-2 activity as well as cytotoxicity in order to find promising anticancer agents having selective Cox-2 inhibitory effect. We determined suppression of PGE_2 production in HCT-116 transfected with Cox-1 and Cox-2 flag cDNA. The level of Cox-1 and Cox-2 inhibition, and Cox-2 selectivity were expressed using inhibition ratio (IR), i.e., ratio of % inhibition of PGE_2 production relative to that of Celecoxib, and selectivity ratio (SR), i.e., IR_{cox-2}/IR_{cox-1}. Cytotoxicity was determined by SRB assay in human lung cancer cell line, A549 and human colon cancer cell line, HT-29. Selected compounds were then evaluated for cell cycle arrest effects. Several compounds having trizole and thiol structure showed $0.78 < IR_{cox-2} < 1.07$ and $1.08 < SR < 23.8$. Among these, three compounds (# 124, 130, 135) showed the activities equivalent to or greater than Celecoxib in respect to Cox-2 inhibition, Cox-2 selectivity, cytotoxicity and cell cycle effect.
Our data demonstrate that (1) Cox-1 and Cox-2 transfected HCT-116 cells may be a useful system for in vitro screening of selective Cox-2 inhibitors and (2) analogues of trizole and thiol may represent a group of promising chemomodulating agents having Cox-2 selectivity and significant cytotoxicity.

[OA-2] [10/18/2002 (Fri) 11:40 - 11:50 / Hall A]

Antitumor activity of oxaliplatin, 5-FU and paclitaxel given alone and in combination with ZD1839 in human gastric carcinoma cells in vitro.

Jang JiHyun°, Lee SangHak, Kang JinHyoung, Sun HeeSik, Kuh HyoJeong

Catholic Research Institutes of Medical Science, The Catholic Univ of Korea, Seoul, Korea.

ZD1839 is a new anticancer agent which selectively inhibits EGFR tyrosine kinase. Oxaliplatin (LOHP), 5-FU (FU), and paclitaxel (PTX) have shown to be highly active against the gastric carcinomas, and ZD1839 is considered as a good candidate for the treatment of gastric cancers when combined with cytotoxic agents. In this study, we evaluated the antitumor effects of these agents in SNU-1 human gastric cancer cells either alone or when given as a doublet. We selected the SNU-1 cells that show MMR deficiency and EGFR overexpression as confirmed by Western blot. Growth inhibition was measured by MTT assay and cell cycle distribution by flow cytometry. The combination index (CI) was used to describe synergistic interaction. The four drugs showed IC_{50}'s ranging from 1.81nM to 13.2μ