## 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

M. LOHP and PTX induced $G_2$/M arrest, 5-FU S phase increase, and ZD1839 $G_1$ increase in a concentration-dependent manner.A previously developed cytostatic TPi model (Jpn J Cancer Res 91:1303) was used to assess the contribution of cell cycle arrest to overall growth inhibition, and 64% and 80% of the overall growth inhibition at $IC_{80}$ after 72hr was attributed to cell cycle arrest for LOHP and PTX, respectively. When combined, PTX+ZD1839 showed the greatest synergism and LOHP+ZD1839 was also synergistic. The cell cycle effect and apoptosis induced by PTX were potentiated by the coadministration of ZD1839. This study demonstrates the antitumor activity of ZD1839 against human gastric carcinoma cells and its synergistic interaction with LOHP and PTX. These results provide a preclinical rationale for future clinical development of ZD1839 and its use in combination with LOHP or PTX against MMR deficient human gastric cancers that express EGFR.

[OA-3] [ 10/18/2002 (Fri) 11:50 - 12:00 / Hall A ]

## Pharmacodynamics of anticancer activity of tirapazamine and paclitaxel against human NSCLC

Park JongKook°, Kang JinHyoung, Kuh HyoJeong

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

Hypoxia in solid tumors is known to contribute to intrinsic chemoresistance. Tirapazamine(TPZ), a hypoxia-selective cytotoxin, showed synergism with radiation or cytotoxic agents. Paclitaxel(PTX) is a highly active anti-cancer agent against Non small cell lung cancer(NSCLC), however, due to poor penetration into central hypoxic region of tumor tissue, combination with TPZ has been suggested to enhance its efficacy. We investigated pharmacodynamics of cytotoxicity, cell cycle arrest and apoptosis induced by TPZ and PTX in monolayers and histocultures of A549 human NSCLC cells. Hypoxic cytotoxicity ratios (HCR) of TPZ in monolayers increased with longer drug exposure. In monolayers, the values of n50(CnxT=k model, at 50% inhibition level) were not greater than 0.5 for TPZ and PTX, indicating greater importance of exposure time than drug conc. In monolayers, TPZ and PTX induced conc-dependent cell cycle arrest(G2/M), and hypoxic condition (2% O2) potentiated cell cycle effect of TPZ by 10 folds compared to normoxic condition. In histocultures, n50 for TPZ was 1.3, indicating greater importance of drug conc than exposure time. Cytotoxicity and cell cycle effect of PTX were significantly reduced in histocultures. However, cell cycle effect induced by TPZ in histocultures was similar to that in monolayers under hypoxia. PTX and TPZ induced apoptosis in cells in G1/S phase and G2/M phase, respectively. These data indicate that (1) pharmacodynamics of TPZ and PTX in monolayers is significantly different from that in 3-dimensional histocultures, which represents in vivo solid tumors, and (2) both TPZ and PTX induced G2/M arrest, but different cell cycle-specific apoptosis was observed. Grant 2000-0-214-001-3 from KSEF.

[OA-4] [ 10/18/2002 (Fri) 12:00 - 12:10 / Hall A ]

## The Differential Roles of Glutamine Synthetase in Methylmercury Neurotoxicity

Park YoungJin°[1,2], Lee SeungTaek[2], Kwon OhSeung[1]

[1]Toxicology Lab., Korea Institute of Science and Technology, Seoul 136-791, and [2]Department of Biochemistry, College of Science, Yonsei University, Seoul 120-749

Methylmercury (MeHg), a potent neurotoxicant, produces neuronal death that may be partially mediated by glutamate. Glutamine synthetase (GS), a glial-specific enzyme, catalyzes the synthesis of glutamine from glutamate and ammonia and is associated with ischemic injury and neurological diseases. Objectives of this experiment are to investigate whether *in vivo* and *in vitro* MeHg exposure have adverse effects on GS and whether duration of exposure to MeHg and glutamate co-treatment play a role in MeHg-induced toxicity. GS activity was measured in cell-free brain homogenate of untreated rats, mice treated with MeHg (2, 4, 10 mg/kg for 1 days), primary cultured glial cells,