[PA1-14] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Antitumor activity and 3D-Histoculture drug response assay of Novel trans-ditrifluoroacetato,malonato-1,4-butanediamine Pt(IV) complex, K104

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Novel trans-ditrifluoroacetato,malonato-1,4-butanediamine Pt(IV) complex, K104 was synthesized as a chemotherpeutic. The cytotoxicity of K104 against various human cancer cell lines were evaluated by MTS assay in vitro. The IC50 values of K104 ranged 15.83-25.83 uM, compared to CBCDA ranged 23.24-69.6 uM. Among several cancer cell lines, K104 showed more potent than CBCDA in colon cancer cell lines. In vivo studies, K104 (30, 50, 100 and 150 mg/kg) was administered by i.p. at day 1, 5, 9 to three animal tumor models compared with CDDP (4 mg/kg) and CBCDA (30 and 60 mg/kg). Antitumor activity (T/C %) of K104 is more potent than CBCDA or CDDP. Especially, K104 showed excellent antitumor activity against BDF1 mice bearing CDDP-resistant cells, L1210/cis-DDP. To evaluate efficacy of K104 against human cancer, the 3D-histoculture drug response assay (HDRA) was performed in 35 cases of colorectal cancer patients. In HDRA, K104 showed 54.3 % efficacy rate compared with 48.6 % of CDDP and 51.4 % of CBCDA against colorectal cancer patient tissues. This study suggests that newly synthesized Pt(IV) complex, K104 appeared to be more effective than CDDP against various antitumor tests.

[PA1-15] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

The effects of the novel IDPc inhibitor, DA-11004, on NADPH generation, insulin secretion, and glucose level in obese diabetic (ob/ ob) mice

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The biological effects of NADPH-dependent isocitrate dehydrogenase (IDPc) inhibitor, DA-11004, was investigated in obese diabetic (ob/ ob) mice. DA-11004, metformin, and oxalomalate were daily injected (ip) for 8 weeks and after completing an 8-week period of experiment, mice were sacrificed at 1hr after the last drugs treatment to collect their blood, liver, and adipose tissues (epididymal and retroperitoneal fat). In the DA-11004 (30mg/kg, ip) treated groups, the increases of body weight and diet consumption were significantly declined when compared to the control groups, but metformin (200mg/kg, ip) or oxalomalate (30mg/kg, ip) had no effects. DA-11004 significantly inhibited the NADPH generation in plasma and synthesis of epididymal and retroperitoneal fat when compared to the control groups ($P<0.01$). Administration of DA-11004 into ob/ob mice decreased the glucose levels or triglycerides levels in both plasma and liver and the GOT, GPT and LDH levels were also significantly decreased in plasma. However, metformin and oxalomalate had no effects on the GOT, GPT, and LDH levels. Metformin decreased the glucose levels, but oxalomalate had no effects in liver. DA-11004 decreased the plasma insulin responses by 50% when compared to control.
In summary, DA-11004 is a synthetic novel IDPc inhibitor, reducing the body weight via inhibition

of fat synthesis and inhibited insulin secretion and declined the glucose and triglycerides levels in plasma.

[PA1-16] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

OST-5440, A Small Molecule Inhibitor of Human Cathepsin K, Inhibits Bone Resorption *In Vivo* as well as *In Vitro*

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Cathepsin K (CK) is a cysteine protease that plays a major and essential role in osteoclast-mediated degradation of collagen matrix of bone. Its tissue-limited distribution and pivotal contribution to bone resorption meet the requirements as the potential therapeutic target of the disease with excessive bone loss such as osteoporosis. In a search for potent CK inhibitors, we found OST-5440 that effectively inhibited bone resorption *in vivo* as well as *in vitro*.
OST-5440 is a synthetic compound that efficiently and selectively inhibits human CK compared with SB357114 as the reference compound. OST-5440 was demonstrated to be superior to SB357114 in selectivity against especially human cathepsin L and bovine cathepsin S which are highly active and closely related to CK, as well as with the comparable IC_{50} value of 2.7 nM against human CK. Moreover OST-5440 efficiently suppressed osteoclast-mediated bone resorption with IC_{50} value of 30 nM in the *in vitro* culture system using unfractionated bone cell isolated from neonatal rabbits.
For the evaluation of *in vivo* efficacy, in the thyroparathyroidectomized (TPTX) rats as an animal model exhibiting the acute bone resorption, orally administered OST-5440 suppressed PTH-induced hypercalcemia as a dose-dependent manner with ED_{50} value of 29 mg/kg, whereas SB357114 showed no significant effect up to 10 mg/kg.
Conclusively, OST-5440 as a potent and selective inhibitor of human CK effectively suppressed bone resorption *in vitro* and *in vivo*, and may propose the therapeutic potential in diseases caused by the excessive bone resorption, such as osteoporosis.

[This study was supported by a grant of the Korea Health 21 R&D Project, Republic of Korea (01-PJ1-PG4-01PT01-0027)]

[PA1-17] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

In vivo metabolism of 2-methylaminoethyl-4,4'-dimethoxy-5,6,5',6'-dimethylenedioxybiphenyl-2'-carboxy-2-carboxylate (DDB-S) in rats using deutrium labeled compound

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2-Methylaminoethyl-4,4'-dimethoxy-5,5',6,6'-dimethylenedioxybiphenyl-2'-carboxy-2-carboxylate (DDB-S), a synthetic compound derived from DDB, has been known to protect liver against carbon tetrachloride-, D-galactosamine-, thioacetamide-, and prednisolone- induced hepatic injury in experimental animals. The metabolism of this compound has been assessed in