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.

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[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

rats by using liquid chromatography/electrospray tandem mass spectrometry (LC/MS/MS) method. Twelve metabolites of DDB-S were identified in the urine and feces. DDB-S consists with two methyledioxy biphenyl moiety and isobaric metabolites of DDB-S were hardly differentiated in MS/MS spectrum. In order to characterize the structure of metabolites, one of each methoxy and methylenedioxy group was selectively exchanged with deutrium and characerization of metabolites were done in rats. The major metabolic pathways of DDB-S in rats were identified as demethylenation of the methylenedioxyphenyl group and demethylation of the carboxymethyl moiety. The others were identified as demethylenation and demethylation, and glucuronidation.

[PA1-18] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Effects of Chlorhexidine digluconate on Rate of Rotational Mobility of Porphyromonas gingivalis Outer Membranes.

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Tempting to further understanding the biophysical mechanism of action of chlorhexidine, we examined effects of the antimicrobial agent(chlorhexidine digluconate) on rate of rotational mobility of liposomes of total lipids extracted from anaerobic bacterial outer membranes (Porphyromonas gingivalis outer membranes). The five fluorescent probes, 2-(9-anthroyloxy) stearic acid(2-AS), 6-(9-anthroyloxy) stearic acid(6-AS), 9-(9-anthroyloxy) stearic acid(9-AS), 12-(9-anthroyloxy) stearic acid(12-AS) and 16-(9-anthroyloxy) palmitic acid(16-AP), were utilized as probes for the surface of the membranes and hydrocarbon interior of the membrane bilayer, respectively. These probes are located at a graded series of depths in the membranes. The AS probes reflect the rate of rotational mobility. Chlorhexidine significantly increased the anisotropy of 2-AS. However chlorhexidine significantly decreased the anisotropies of 6-AS, 9-AS, 12-AS and 16-AP. These results indicate that the rate of rotational diffusion changes resulted from the interaction between chlorhexidine digluconate and outer membrane lipid bilayer are important in the biophysical mechanism of action of chlorhexidine digluconate.

[PA1-19] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Estrogen receptor expression and behavioral changes in immature mice treated with bisphenol A

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A large number of chemical pollutants including phthalates, alkylphenolic compounds, organochlorine pesticides and bisphenol A have the ability to disrupt endocrine function in animals, and alter cognitive function. Because hormone mediated events play a important role in central nervous system development and functions. The speculations that the changes in cognitive function are mediated by the endocrine-like action of these chemicals. The present study therefore was designed to investigate effect of bisphenol A (BPA), an endocrine disrupting chemical on neuro-behavior patterns, and expression of estrogen receptors and tyrosine hydroxylase, a limiting enzyme of dopamine synthesis pathway. BPA was treated orally for 3 weeks into 3 week old rats, and then the neuro-behavior patterns (stereotype behaviors such as jumping rearing and forepaw tremor, climbing behavior, tail flick, rotarod and locomotor activity), and the expression of estrogen receptors and tyrosine hydroxylase were determined every 3