東京医科歯科大学

Global COE Program
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歯と骨の分子疾患科学の国際教育研究拠点
ーデント・メドミクスのインテリジェンスハブー

第4回GCOE海外研究者招聘講演会
第208回 Bone Biology Seminar

講師：Dr. Le Thi Duong, Ph.D.

日時：平成20年7月30日（水）
15：00 ～17：00

Cathepsin K Inhibitors: From the Bench to the Clinic

Cathepsin K (Cat K) is a lysosomal cysteine protease that is highly expressed in osteoclasts and plays a critical role in the degradation of bone collagen. Cat K is unique in its ability to cleave at multiple sites within the native collagen trimer in both the non-helical and the proteolytically resistant helical region. The human disease characterized by cathepsin K gene mutations is known as pycnodysostosis, a rare autosomal-recessive osteochondrodysplasia. There are several mouse lines in which the Cat K gene has been deleted; all exhibit defects in bone resorption, without affecting osteoclast number. Histomorphometric analysis of cancellous regions of femoral bones from Cat K-deficient mice shows an increased bone formation rate. We achieved preclinical proof of principal that small molecular weight, orally-active and reversible inhibitors of Cat K are effective anti-resorptive agents for the prevention of estrogen-deficient induced bone loss in rabbit and monkey. Odanacatib (MK-0822), a selective Cat K inhibitor that does not take up residence in bone, has been shown to rapidly and reversibly decrease bone resorption in both preclinical and 18-month clinical studies. Odanacatib has an IC50 of 0.2 nM against human Cat K, and is 300-fold selective versus Cat S and >5000-fold selective versus other cathepsins. In a functional bone resorption assay using rabbit osteoclasts, odanacatib has an IC50 of 23 ± 6 nM. This compound has an excellent pharmacokinetic profile in multiple preclinical species. In preclinical models, odanacatib has demonstrated dose-dependent increases in bone mineral density (BMD) and suppression of bone turnover markers in OVX rhesus monkeys. Based on Phase I results, the pharmacokinetic profile supports weekly dosing of this drug. Subsequently, odanacatib treatment for 12 months in post menopausal women with low BMD was reported to be generally safe and well tolerated, and effectively suppressed bone turnover markers and increased lumbar spine and femoral neck BMD. 18-month results from this study will be shared at this meeting. These preclinical and clinical data suggest that odanacatib may be developed as an effective therapeutic agent for the treatment of diseases associated with bone loss including osteoporosis, metastatic bone disease and osteoarthritis.

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