BoneKEy-Osteovision. 2006 August;3(8):1-4
http://www.bonekey-ibms.org/cgi/content/full/ibmske;3/8/1
DOI: 10.1138/20060223

# *NOT TO BE MISSED*

# Clinical and Basic Research Papers – July 2006 Selections

## Serge Ferrari, Associate Editor
## Ego Seeman, Clinical Editor
## Gordon J. Strewler, Editor

### Bone Modeling and Remodeling

Allison SJ, Baldock P, Sainsbury A, Enriquez R, Lee NJ, Lin EJ, Klugman M, During M, Eisman JA, Li M, Pan LC, Herzog H, Gardiner EM. Conditional deletion of hypothalamic Y2 receptors reverts gonadectomy-induced bone loss in adult mice. *J Biol Chem*. 2006 Aug 18;281(33):23436-44. [Abstract] [Full Text]

> *Conditional deletion of neuropeptide Y2 receptors prevents bone loss in sex-hormone deficiency due to activation of bone formation, suggesting the Y2-mediated anabolic pathway to be independent of sex hormones. The increase in fat mass that occurs after ovariectomy is prevented by germline deletion of Y2-receptors, while in male mice weight and fat mass are lower than wild-type regardless of sex hormone status. Y2-receptors accumulate adipose tissue in the hypogonadal state, hypothalamic Y2-receptors restrain osteoblastic activity. The increase in bone formation after release of this inhibition suggests an avenue for treatment.* —ES

Bliziotes M, Sibonga JD, Turner RT, Orwoll E. Periosteal remodeling at the femoral neck in nonhuman primates. *J Bone Miner Res*. 2006 Jul;21(7):1060-7. [Abstract]

> *The periosteum is thought to be mainly a bone forming surface but this is not the case, at least in this animal model. Femur specimens from 16 intact adult male and female nonhuman primates showed periosteal remodeling of the femoral neck in intact animals was more rapid than at the femoral shaft but slower than in femoral neck cancellous bone. Eroded surface at the femoral neck periosteal surface was greater than in the cancellous bone compartment or on the femoral shaft. Gonadectomized females showed an increase in osteoclast number on the periosteal surface compared with intact controls.* —ES

Rodda SJ, McMahon AP. Distinct roles for Hedgehog and canonical Wnt signaling in specification,differentiation and maintenance of osteoblast progenitors. *Development*. 2006 Aug;133(16):3231-44. [Abstract]

> *Sequential signaling by Hedgehog and the canonical Wnt pathway is required for osteoblast development. In this paper signaling through these pathways was modulated late in osteoblast development by conditional mutagenesis with osterix-cre. Removal of Ihh at this stage has little effect; the earlier requirement for Ihh is therefore transient. By contrast, eliminating Wnt signaling prevents osteoblasts from maturing and enhanced Wnt signaling massively increases osteoblast formation, producing dense bone where the primary spongiosa should be. Removal of Wnt7b has little effect: the Wnt that makes osteoblasts has yet to be spotted.* —GJS

## Treatment and Drug Effects

Allen MR, Iwata K, Sato M, Burr DB. Raloxifene enhances vertebral mechanical properties independent of bone density. *Bone*. 2006 Jun 28; [Epub ahead of print] [Abstract]

> *This study illustrates that the material and structural basis of bone strength is poorly defined. Non-ovariectomized female beagles were treated for 12 months with risedronate, alendronate, raloxifene or saline. RAL suppressed remodeling (-20%) less than the bisphosphonates (-66 and -71%) and did not change aBMD, vBMD, BV/TV or percent ash. Microdamage in RAL-treated animals was not different than VEH; RIS and ALN had higher crack surface density. Stiffness was higher than VEH in all groups. Ultimate load divided by aBMD was higher in RAL-treated animals. Raloxifene improves bone mechanical properties independently of BMD; it's just not clear how.* —ES

Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK; Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006 Jul 13;355(2):125-37. [Abstract]

> *The notion of risk benefit ratios is emphasized in this study in which 10,101 postmenopausal women were followed for a median of 5.6 years. Raloxifene reduced the risk of invasive breast cancer and clinical vertebral fractures but increased risk of fatal stroke and venous thrombo-embolism. There was no alteration in risk for coronary events.* —ES

Iwata K, Li J, Follet H, Phipps RJ, Burr DB. Bisphosphonates suppress periosteal osteoblast activity independently of resorption in rat femur and tibia. *Bone*. 2006 Jun 23; [Epub ahead of print] [Abstract]

> *Periosteal apposition increases resistance to bending and if suppressed may limit whatever little adaptive potential bone formation on this surface may have in the face of endosteal bone loss. Risedronate or alendronate were administered to 6-month-old female Sprague-Dawley rats. In the femur, periosteal MAR was reduced by 22-29% for risedronate and 26-36% for alendronate. In the tibia, periosteal MAR and BFR of all treatment groups were lower (41-50% for risedronate, 43-52% for alendronate than in the controls). Bisphosphonates may affect the activity of individual osteoblasts.* —ES

Kim HJ, Zhao H, Kitaura H, Bhattacharyya S, Brewer JA, Muglia LJ, Ross FP,Teitelbaum SL. Glucocorticoids suppress bone formation via the osteoclast. *J Clin Invest*. 2006 Aug;116(8):2152-60. [Abstract] [Full Text]

> *Glucocorticoid osteoporosis has been linked to defective osteoblast function and premature osteoblast apoptosis; the role of osteoclasts in the disorder has been controversial. Here, glucocorticoids are shown to inhibit osteoclast spreading and function in vitro; removal of the glucocorticoid receptor from osteoclasts prevents these changes and also prevents 14 days of dexamethasone treatment from inhibiting mineral apposition rate and serum markers of bone formation. The results open a window on crosstalk between osteoclasts and osteoblasts.* —GJS

Martyn-St James M, Carroll S. High-intensity resistance training and postmenopausal bone loss: a meta-analysis. *Osteoporos Int*. 2006 Aug;17(8):1225-40. [Abstract]

*This meta-analysis is worth reading for what is lacking – evidence of anti-fracture efficacy. The endpoints are BMD. The methodological quality of the data available for analysis is low and whatever small differences in BMD may mean in terms of fracture risk reduction is difficult to determine. But lack of evidence should not deter faith in bias and opinion.* —ES

## Reviews, Perspectives and Editorials

Hernandez CJ, Keaveny TM. A biomechanical perspective on bone quality. *Bone*. 2006 Jul 27; [Epub ahead of print] [Abstract]

Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest*. 2006 Aug;116(8): 2062-72. [Abstract] [Full Text]

Taylor EN, Curhan GC. Diet and fluid prescription in stone disease. *Kidney Int*. 2006 Jul 12; [Epub ahead of print] [Abstract]

## Other Studies of Potential Interest

Aharon R, Bar-Shavit Z. Involvement of aquaporin 9 in osteoclast differentiation. *J Biol Chem*. 2006 Jul 14;281(28):19305-9. [Abstract] [Full Text]

Aronson PS. Essential roles of CFEX-mediated Cl(-)-oxalate exchange in proximal tubule NaCl transport and prevention of urolithiasis. *Kidney Int*. 2006 Aug 2; [Epub ahead of print] [Abstract]

Bounoutas GS, Tawfeek H, Frohlich LF, Chung UI, Abou-Samra AB. Impact of impaired receptor internalization on calcium homeostasis in knock-in mice expressing a phosphorylation-deficient parathyroid hormone (PTH)/PTH-related peptide receptor. *Endocrinology*. 2006 Jul 13; [Epub ahead of print]

Burnett SA, Gunawardene SC, Bringhurst FR, Juppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. *J Bone Miner Res*. 2006 Aug;21(8):1187-96. [Abstract]

Edwards JC, Cohen C, Xu CW, Schlesinger PH. C-Src control of chloride channel support for osteoclast HCL transport and bone resorption. *J Biol Chem*. 2006 Jul 10; [Epub ahead of print]

Fitzgerald JB, Jin M, Grodzinsky AJ. Shear and compression differentially regulate clusters of functionally-related temporal transcription patterns in cartilage tissue. *J Biol Chem*. 2006 Aug 25;281(34):24095-24103. [Abstract] [Full Text]

Hernandez CJ, Gupta A, Keaveny TM. A biomechanical analysis of the effects of resorption cavities on cancellous bone strength. *J Bone Miner Res*. 2006 Aug;21(8):1248-55. [Abstract]

Li M, Hener P, Zhang Z, Kato S, Metzger D, Chambon P. Topical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis. *Proc Natl Acad Sci U S A*. 2006 Aug 1;103(31):11736-41. [Abstract] [Full Text]

Robertson KM, Norgard M, Windahl SH, Hultenby K, Ohlsson C, Andersson G, Gustafsson JA. Cholesterol-sensing receptors, liver X receptor alpha and beta, have novel and distinct roles in osteoclast differentiation and activation. *J Bone Miner Res*. 2006 Aug;21(8):1276-87. [Abstract]

Simic P, Buljan Culej J, Orlic I, Grgurevic L, Draca N, Spaventi R, Vukicevic S. Systemically administered bone morphogenetic protein-6 restores bone in aged ovx rats by increasing bone formation and suppressing bone resorption. *J Biol Chem*. 2006 Jun 23; [Epub ahead of print]

Wang L, Hinoi E, Takemori A, Nakamichi N, Yoneda Y. Glutamate inhibits chondral mineralization through apoptotic cell death mediated by retrograde operation of the cystine/glutamate antiporter. *J Biol Chem*. 2006 Aug 25;281(34):24553-24565. [Abstract] [Full Text]

Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo MO, Young SG, Fong LG. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. *J Clin Invest*. 2006 Jul 20; [Epub ahead of print]

**Conflict of Interest:** Dr. Ferrari and Dr. Strewler report that no conflicts of interest exist. Dr. Seeman reports that he is an advisory committee member for Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies.