

NOT TO BE MISSED

Clinical and Basic Research Papers – May 2008

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Bone Modeling, Remodeling and Repair

◆ DeMambro VE, Clemmons DR, Horton LG, Bouxsein ML, Wood TL, Beamer WG, Canalis E, Rosen CJ. Gender-specific changes in bone turnover and skeletal architecture in igfbp-2-null mice. *Endocrinology*. 2008 May;149(5):2051-61. [[Abstract](#)] [[Full Text](#)]

IGFBP-2 has a high affinity for extracellular matrices containing glycosaminoglycans, and may serve to target IGFs to bone. Skeletal phenotypes of IGFBP-2(-/-) mice were compared with those of WT mice to clarify the role of IGFBP-2 on bone turnover and mass. In WT mice, serum IGFBP-2 levels were higher in males than in females by more than 40%. In IGFBP-2(-/-) mice, only males showed reduced trabecular bone volume and thickness. Cellular phosphatase and tensin homolog (PTEN) was elevated in IGFBP-2(-/-) males. Because PTEN interferes with IGF signaling, the reduced serum IGFBP-2 levels along with increased PTEN expression in IGFBP-2(-/-) males may explain part of the gender difference in bone mass, at least in trabecular bone. However, the increase in cortical bone area and size in IGFBP-2(-/-) females requires further examination. —TM

◆ Kramer I, Kneissel M. The high bone mass phenotype of *Sost* deficient mice is characterized by progressive increase in bone thickness, mineralization and predicted cortical bone strength in a gene dosage unrelated manner. *Bone*. 2008 Mar;42(Suppl 1):S57.

*Presented at the IBMS Davos Workshops: Bone Biology & Therapeutics, the Novartis group show that heterozygous knockout of *Sost* (as well as homozygous KO) is anabolic, with a clear gene dosing effect. In female mice at 14 weeks, *Sost*(-/-) mice displayed 1.7-fold increases in microCT-derived total BMD, while *Sost*(+/-) mice exhibited 1.3-fold increases over WT. Trabecular thickness was also increased but in this circumstance the *Sost*(+/-) mice demonstrated a 1.3-fold increase while a much larger increase was noted in *Sost*(-/-) mice. Cancellous BMD increased over time up to 4-fold compared to WT mice. Cortical thickness increased progressively up to 2.5-fold in *Sost*(-/-) mice compared to WT mice. Cortical bone gain was related to increases in periosteal circumference coupled with decreased endocortical circumference. Polar moment of inertia increased up to 2.7-fold in *Sost*(-/-) mice. Although the heterozygous mice display a phenotype, it was solely gene dosing-dependent, with modest changes in *Sost*(+/-) mice. This study is in broad agreement with the study by Li et al. (see March 2008 [Not To Be Missed](#)) regarding the anabolic potential of sclerostin deficiency. —DGL*

Clinical Studies and Drug Effects

◆ Corrado A, Quarta L, Errico S, Cantatore FP. Successful treatment of avascular bone necrosis of the knee with neridronate: a case report. *Rheumatol Int*. 2007 Jul;27(9):891-3. [[Info](#)]

This is a case report of rapid reduction in bone marrow edema and pain in a case of osteonecrosis of the knee. Given that SONK can either be progressive or can resolve, clinical trials to determine the benefit of bisphosphonates over the natural history are required. Better studies are needed to determine if bisphosphonates can alter the outcome in spontaneous osteonecrosis of the knee and the related entity of subchondral insufficiency fracture. —DGL

- ◆Fuchs RK, Allen MR, Condon KW, Reinwald S, Miller LM, McClenathan D, Keck B, Phipps RJ, Burr DB. Strontium ranelate does not stimulate bone formation in ovariectomized rats. *Osteoporos Int*. 2008 Apr 3; [Epub ahead of print] [\[Abstract\]](#)

Three-month old rats underwent ovariectomy and, 4 weeks later, were treated with SrR (25 or 150 mg/kg/day) plus a low (0.1%) or normal (1.19%) calcium (Ca) diet. SrR did not increase trabecular or periosteal bone formation and failed to inhibit resorption of trabecular bone. There were no improvements in bone mass or strength. —ES

- ◆Saito M, Mori S, Mashiba T, Komatsubara S, Marumo K. Collagen maturity, glycation induced-pentosidine, and mineralization are increased following 3-year treatment with incadronate in dogs. *Osteoporos Int*. 2008 Mar 29; [Epub ahead of print] [\[Abstract\]](#)

Twenty-nine 1-year-old beagles treated with incadronate (0.3 or 0.6 mg/kg/day for 3 years) had increased calcium, phosphorus, and pentosidine content, and an increased ratio of mature/immature cross-links, but normal total enzymatic cross-links. Pentosidine content correlated inversely with cortical activation frequency ($p < 0.01$). Long-term suppression of bone remodeling by bisphosphonate increases degree of mineralization, collagen maturity, and non-enzymatic cross-linking. —ES

- ◆Takeda M, Higuchi H, Kimura M, Kobayashi Y, Terauchi M, Takagishi K. Spontaneous osteonecrosis of the knee: histopathological differences between early and progressive cases. *J Bone Joint Surg Br*. 2008 Mar;90(3):324-9. [\[Abstract\]](#)

In this prospective biopsy study of 20 patients with osteonecrosis of the knee, early lesions can be seen to involve a subchondral fracture without areas of osteonecrosis between the fracture line and articular surface. The authors stress that small amounts of osteonecrosis are always seen next to any fracture; these are discounted and larger areas of osteonecrosis only considered as primary. Later lesions involve necrotic bone between the subchondral fracture and often display fibrocartilagenous tissue and osteoid in the gap, indicating unsuccessful attempts at repair. This paper highlights that in spontaneous osteonecrosis of the knee with no secondary causation such as steroids, the subchondral fracture is the likely initiating event. —DGL

- ◆Yates PJ, Calder JD, Stranks GJ, Conn KS, Peppercorn D, Thomas NP. Early MRI diagnosis and non-surgical management of spontaneous osteonecrosis of the knee. *Knee*. 2007 Mar;14(2):112-6. [\[Abstract\]](#)

Early cases of spontaneous osteonecrosis of the knee were treated with restricted weight bearing and NSAIDs. All cases were grade I and had small lesions. In all cases pain resolved in 4-8 months and MRI changes also resolved, though some took up to 18 months. —DGL

Genetics

- ◆Jepsen K, Price C, Silkman L, Nicholls F, Nasser P, Hu B, Hadi N, Alapatt M, Stapleton S, Kakar S, Einhorn T, Gerstenfeld L. Genetic variation in the patterns of skeletal progenitor cell differentiation and progression during endochondral bone formation affects the rate of fracture healing. *J Bone Miner Res.* 2008 Mar 18; [Epub ahead of print] [\[Abstract\]](#)

How are genetic differences that regulate architectural and bone material properties expressed during fracture healing, and do any of these features affect rates of healing? Controlled fracture healing experiments were undertaken in three inbred strains of mice. Two strains showed fast healing based on regains in strength and stiffness. One strain expressed the highest percentage of cartilage gene products and had the longest period of chondrocyte maturation and hypertrophy. The three inbred strains also had differences in other features including: fracture healing in the period of chondrogenic development, the initiation of osteogenic development, growth plate heights, cell numbers per column and cell size. These results indicate that different strains of mice express variations of skeletal stem cell lineage differentiation and that these variations affect the rate of fracture healing. —HWD

- ◆Richards JB, Rivadeneira F, Inouye M, Pastinen TM, Soranzo N, Wilson SG, Andrew T, Falchi M, Gwilliam R, Ahmadi KR, Valdes AM, Arp P, Whittaker P, Verlaan DJ, Jhamai M, Kumanduri V, Moorhouse M, van Meurs JB, Hofman A, Pols HA, Hart D, Zhai G, Kato BS, Mullin BH, Zhang F, Deloukas P, Uitterlinden AG, Spector TD. Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. *Lancet.* 2008 May 3;371(9623):1505-12. [\[Abstract\]](#)

If you want to know more about the sequence variants associated with osteoporosis phenotypes, you should not miss this genome-wide association study (GWAS). This study identified genome-wide evidence for associations of two SNPs with BMD, osteoporosis and osteoporotic fracture. The two SNPs are near the TNFRSF11B (osteoprotegerin) gene, and the LRP5 (lipoprotein receptor-related protein) gene. The identified risk alleles justify further clinical and biological investigations. —HWD

- ◆Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, Gudbjartsson DF, Walters GB, Ingvarsson T, Jonsdottir T, Saemundsdottir J, Center JR, Nguyen TV, Bagger Y, Gulcher JR, Eisman JA, Christiansen C, Sigurdsson G, Kong A, Thorsteinsdottir U, Stefansson K. Multiple genetic loci for bone mineral density and fractures. *N Engl J Med.* 2008 Apr 29; [Epub ahead of print]

This GWAS reported that associations of five genomic regions with BMD and fractures were replicated consistently in three replication sets of subjects of European descent (Danish, Australian and Icelandic subjects). The four loci 1p36, 6q25, 8q24 and 13q14 influence BMD at both the spine and the hip, and 6p21 is associated with BMD at the spine only. The three regions 6q25, 8q24 and 13q14 are close to or within genes previously shown to be important to the biologic characteristics of bone: RANKL, OPG, and ESR1, respectively. —HWD

Molecular and Cell Biology

- ◆Ono N, Nakashima K, Rittling SR, Schipani E, Hayata T, Ezura Y, Soma K, Denhardt DT, Kronenberg HM, Noda M. Osteopontin negatively regulates parathyroid hormone receptor signaling in osteoblasts. *J Biol Chem.* 2008 Apr 16; [Epub ahead of print]

Transgenic mice expressing a constitutively active form of the PTH receptor (caPPR) in osteoblast lineage cells have a high bone mass phenotype. OPN deficiency increased

bone mass further with conversion of the intertrabecular cell population from hematopoietic to stromal/osteoblastic cells producing increases in histomorphometric and biochemical parameters of bone formation and resorption. Treatment with siRNA for osteopontin enhanced H223R mutant caPPR-induced cAMP-response element (CRE) activity levels by about ten-fold. Thus, local feedback regulation by OPN regulates PTH actions. —ES

- ◆Sabatakos G, Rowe GC, Kveiborg M, Wu M, Neff L, Chiusaroli R, Philbrick WM, Baron R. Doubly truncated FosB isoform (Delta2DeltaFosB) induces osteosclerosis in transgenic mice and modulates expression and phosphorylation of Smads in osteoblasts independent of intrinsic AP-1 activity. *J Bone Miner Res.* 2008 May;23(5):584-95. [\[Abstract\]](#)

Transgenic mice overexpressing Δ FosB, a C-terminal truncated splice variant of FosB lacking transactivation domains, develop severe and progressive osteosclerosis. The authors demonstrated that transgenic mice overexpressing $\Delta 2\Delta$ FosB also exhibited osteosclerosis and reduced fat mass. Because $\Delta 2\Delta$ FosB is both a C-terminal and N-terminal truncated isoform of FosB, lacking Fos homology domains as well as transactivation domains but retaining DNA-binding and leucine zipper motifs, it does not retain transactivation function. Overexpression of $\Delta 2\Delta$ FosB also enhanced expression, phosphorylation and nuclear translocation of Smad1, and stimulated expression of BMP-responsive genes. These results provide evidence that AP-1 transcriptional activity is not needed for the induction of high bone mass, and that the osteogenic effect of $\Delta 2\Delta$ FosB is mediated at least in part by the enhanced expression and activation of Smad1 signaling. —TM

Physiology and Metabolism

- ◆Ferron M, Hinoi E, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. *Proc Natl Acad Sci U S A.* 2008 Apr 1;105(13):5266-70. [\[Abstract\]](#) [\[Full Text\]](#)

Cell-based assays using isolated pancreatic islets and primary adipocytes showed that picomolar amounts of osteocalcin regulate expression of the insulin genes and β cell proliferation markers whereas nanomolar amounts affect adiponectin in white adipocytes and Pgc1 α expression in brown adipocytes. Treatment of WT mice with osteocalcin lessened the deleterious effect of gold thioglucose-induced hyperphagia and high-fat diet on body mass and glucose metabolism. Osteocalcin is important in regulating glucose metabolism and fat mass and may be a treatment for metabolic diseases. —ES

- ◆Vicent S, Luis-Ravelo D, Antón I, García-Tuñón I, Borrás-Cuesta F, Dotor J, De Las Rivas J, Lecanda F. A novel lung cancer signature mediates metastatic bone colonization by a dual mechanism. *Cancer Res.* 2008 Apr 1;68(7):2275-85. [\[Abstract\]](#)

Using a xenograft model of a large cell lung carcinoma cell line with an ability to induce aggressive osseous lesions, transcriptomic analysis identified genes encoding signaling molecules TCF4 and PRKD3 (PKC ν), and cell anchorage-related proteins MCAM (CD146) and SUSD5. TGF- β and tumor-stromal cell interaction enhanced the expression of most of these genes. Triple gene combinations (SUSD5/TCF4/PRKD3 and MCAM/TCF4/PRKD3) markedly enhanced osteoclastogenesis and metalloproteolytic activities, which were associated with robust bone colonization but did not affect tumor growth or cell homing to bone. This novel prometastatic gene signature may mediate tumor bone colonization by a cooperative contribution of TGF- β -dependent osteoclastic osteolysis and stroma-dependent metalloproteolytic activities. —TM

Reviews, Perspectives and Editorials

◆Carbonell Sala S, Brandi ML. 2006 update on genetic determinants of osteoporosis. *J Endocrinol Invest.* 2007;30(6 Suppl):2-7. [\[Abstract\]](#)

Other Studies of Potential Interest

◆Allan EH, Häusler KD, Wei T, Gooi JH, Quinn JM, Crimeen-Irwin B, Pompolo S, Sims NA, Gillespie MT, Onyia JE, Martin TJ. EphrinB2 regulation by parathyroid hormone (PTH) and PTHrP revealed by molecular profiling in differentiating osteoblasts. *J Bone Miner Res.* 2008 Apr 14; [Epub ahead of print] [\[Abstract\]](#)

◆Del Fattore A, Fornari R, Van Wesenbeeck L, de Freitas F, Timmermans JP, Peruzzi B, Cappariello A, Rucci N, Spera G, Helfrich MH, Van Hul W, Migliaccio S, Teti A. A new heterozygous mutation (R714C) of the osteopetrosis gene, pleckstrin homolog domain containing family M (with run domain) member 1 (PLEKHM1), impairs vesicular acidification and increases TRACP secretion in osteoclasts. *J Bone Miner Res.* 2008 Mar;23(3):380-91. [\[Abstract\]](#)

◆Funk JL, Chen J, Downey KJ, Clark RA. Bone protective effect of simvastatin in experimental arthritis. *J Rheumatol.* 2008 May 1; [Epub ahead of print] [\[Abstract\]](#)

◆Jiang LS, Zhang ZM, Jiang SD, Chen WH, Dai LY. Differential bone metabolism between postmenopausal women with osteoarthritis and osteoporosis. *J Bone Miner Res.* 2008 Apr;23(4):475-83. [\[Abstract\]](#)

◆Jin W, Chang M, Paul EM, Babu G, Lee AJ, Reiley W, Wright A, Zhang M, You J, Sun SC. Deubiquitinating enzyme CYLD negatively regulates RANK signaling and osteoclastogenesis in mice. *J Clin Invest.* 2008 May 1;118(5):1858-66. [\[Abstract\]](#)

◆Pace JM, Wiese M, Drenguis AS, Kuznetsova N, Leikin S, Schwarze U, Chen D, Mooney SH, Unger S, Byers PH. Defective C-propeptides of the PROalpha 2(I) chain of type I procollagen impede molecular assembly and result in osteogenesis imperfecta. *J Biol Chem.* 2008 Mar 27; [Epub ahead of print]

◆Pan F, Xiao P, Guo Y, Liu YJ, Deng HY, Recker RR, Deng HW. Chromosomal regions 22q13 and 3p25 may harbor quantitative trait loci influencing both age at menarche and bone mineral density. *Hum Genet.* 2008 May;123(4):419-27. [\[Abstract\]](#)

◆Sheng MH, Wergedal JE, Mohan S, Lau KH. Osteoactivin is a novel osteoclastic protein and plays a key role in osteoclast differentiation and activity. *FEBS Lett.* 2008 Apr 30;582(10):1451-8. [\[Abstract\]](#)

◆Sims AM, Shephard N, Carter K, Doan T, Dowling A, Duncan EL, Eisman J, Jones G, Nicholson G, Prince R, Seeman E, Thomas G, Wass JA, Brown MA. Genetic analyses in a sample of individuals with high or low BMD shows association with multiple Wnt pathway genes. *J Bone Miner Res.* 2008 Apr;23(4):499-506. [\[Abstract\]](#)

◆Tenne M, McGuigan F, Jansson L, Gerdhem P, Obrant KJ, Luthman H, Akesson K. Genetic variation in the PTH pathway and bone phenotypes in elderly women: evaluation of PTH, PTHLH, PTHR1 and PTHR2 genes. *Bone.* 2008 Apr;42(4):719-27. [\[Abstract\]](#)

- ◆Ueki M, Tanaka N, Tanimoto K, Nishio C, Honda K, Lin YY, Tanne Y, Ohkuma S, Kamiya T, Tanaka E, Tanne K. The effect of mechanical loading on the metabolism of growth plate chondrocytes. *Ann Biomed Eng.* 2008 May;36(5):793-800. [\[Abstract\]](#)
- ◆Wang XL, Deng FY, Tan LJ, Deng HY, Liu YZ, Papasian CJ, Recker RR, Deng HW. Bivariate whole genome linkage analyses for total body lean mass and BMD. *J Bone Miner Res.* 2008 Mar;23(3):447-52. [\[Abstract\]](#)
- ◆Wehrli FW, Ladinsky GA, Jones C, Benito M, Magland J, Vasilic B, Popescu AM, Zemel B, Cucchiara AJ, Wright AC, Song HK, Saha PK, Peachey H, Snyder PJ. In vivo magnetic resonance detects rapid remodeling changes in the topology of the trabecular bone network after menopause and the protective effect of estradiol. *J Bone Miner Res.* 2008 May;23(5):730-40. [\[Abstract\]](#)
- ◆Xiao P, Chen Y, Jiang H, Liu YZ, Pan F, Yang TL, Tang ZH, Larsen JA, Lappe JM, Recker RR, Deng HW. In vivo genome-wide expression study on human circulating B cells suggests a novel ESR1 and MAPK3 network for postmenopausal osteoporosis. *J Bone Miner Res.* 2008 May;23(5):644-54. [\[Abstract\]](#)
- ◆Yu S, Cantorna MT. The vitamin D receptor is required for iNKT cell development. *Proc Natl Acad Sci U S A.* 2008 Apr 1;105(13):5207-12. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Yu S, Jiang Y, Galson DL, Luo M, Lai Y, Lu Y, Ouyang HJ, Zhang J, Xiao G. General transcription factor IIA-gamma increases osteoblast-specific osteocalcin gene expression via activating transcription factor 4 and runt-related transcription factor 2. *J Biol Chem.* 2008 Feb 29;283(9):5542-53. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Zhang Q, Guo R, Lu Y, Zhao L, Zhou Q, Schwarz EM, Huang J, Chen D, Jin ZG, Boyce BF, Xing L. VEGF-C, a lymphatic growth factor, is a RANKL target gene in osteoclasts that enhances osteoclastic bone resorption through an autocrine mechanism. *J Biol Chem.* 2008 May 9;283(19):13491-9. [\[Abstract\]](#) [\[Full Text\]](#)

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. 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. Dr. Matsumoto and Dr. Deng report no conflicts of interest.