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NOT TO BE MISSED

Clinical and Basic Research Papers – November 2008

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Toshio Matsumoto, Associate Editor

Bone Modeling, Remodeling and Repair

Blain H, Chavassieux P, Portero-Muzy N, Bonnel F, Canovas F, Chammas M, Maury P, Delmas PD. Cortical and trabecular bone distribution in the femoral neck in osteoporosis and osteoarthritis. *Bone*. 2008 Nov;43(5):862-8. [Abstract]

> *There are well-known differences in hip fracture risk between patients with OA of the hip and osteoporosis. From human biopsies taken at the time of arthroplasty, this study reveals that in addition to cortical thinning, loss of trabecular bone mass and connectivity plays a role in the skeletal fragility associated with hip fracture.* —DGL

Courtland HW, Nasser P, Goldstone AB, Spevak L, Boskey AL, Jepsen KJ. Fourier transform infrared imaging microspectroscopy and tissue-level mechanical testing reveal intraspecies variation in mouse bone mineral and matrix composition. *Calcif Tissue Int*. 2008 Nov;83(5):342-53. [Abstract]

> *Sixteen-week-old female A/J, B6, and C3H inbred mouse femora were analyzed using Fourier transform infrared imaging. A/J femora had an increased mineral-to-matrix ratio compared to B6. The C3H mineral-to-matrix ratio was intermediate. C3H had reduced acid phosphate and carbonate levels and an increased collagen cross-link ratio compared to A/J and B6. A/J were the most stiff, B6 being the least, and C3H intermediate. In addition, highly mineralized and brittle A/J had the least amount of work-to-failure.* —ES

Patel ZS, Young S, Tabata Y, Jansen JA, Wong ME, Mikos AG. Dual delivery of an angiogenic and an osteogenic growth factor for bone regeneration in a critical size defect model. *Bone*. 2008 Nov;43(5):931-40. [Abstract]

> *In tissue engineering it seems desirable to induce vasculature and recruit cells as well as to have a specific osteogenic stimulus to promote differentiation and bone production. In this cranial defect study, VEGF alone, BMP-2 alone and the combination of the two were compared to control defects. VEGF alone increased vessel formation but did not provide a specific bone stimulus, so healing did not occur. VEGF added to BMP-2 increased bone formation at 4 weeks over BMP-2 alone but not at 12 weeks. It remains unclear if the pro-angiogenic and cell recruitment properties of BMP-2 are enough alone or whether augmenting with VEGF is needed.* —DGL

Ritchie RO, Koester KJ, Ionova S, Yao W, Lane NE, Ager JW 3rd. Measurement of the toughness of bone: a tutorial with special reference to small animal studies. *Bone*. 2008 Nov;43(5):798-812. [Abstract]

Biomechanical techniques for characterizing bone strength are well-documented. This review/tutorial shifts the focus to measuring fracture toughness, i.e., bone's resistance to fracture, with respect to whole bone testing in small animal studies. Optimizing the variability of measurements means smaller numbers of animals need to be tested to provide meaningful information. —DGL

Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D. Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. *Osteoporos Int*. 2008 Oct 11; [Epub ahead of print] [Abstract]

Non-enzymatic glycation results in the formation of advanced glycation end-products (AGEs). Vehicle (VEH), alendronate (ALN 0.20, 1.00 mg/kg) or risedronate (RIS 0.10, 0.50 mg/kg) was administered using a canine animal model. Accumulation of AGEs was produced at high treatment doses (+49 to +86%; $p < 0.001$), compared to vehicle. Postyield work-to-fracture was reduced at high doses (-28% to -51%; $p < 0.001$). AGE accumulation inversely correlated with postyield work-to-fracture ($r^2 = 0.45$; $p < 0.001$). Bisphosphonates given at high doses result in accumulation of AGEs and a reduction in energy absorption of cortical bone. —ES

Vashishth D. Small animal bone biomechanics. *Bone*. 2008 Nov;43(5):794-7. [Abstract]

This editorial on small animal bone mechanical testing updates us on efforts being made to reduce variations in mechanical testing of small animal bones. Under the correct conditions, notched specimens can provide a comprehensive set of evaluations of the material, and not just geometric, properties of small animal bones. —DGL

Cancer and Bone

Fournier PG, Daubiné F, Lundy MW, Rogers MJ, Ebetino FH, Clézardin P. Lowering bone mineral affinity of bisphosphonates as a therapeutic strategy to optimize skeletal tumor growth inhibition in vivo. *Cancer Res*. 2008 Nov 1;68(21):8945-53. [Abstract]

Pursuing their seminal work in this area, these authors show here that a bisphosphonate with very low affinity for bone reduces skeletal tumor growth in a mouse model of human breast cancer bone metastasis much more effectively than the high affinity bisphosphonate risedronate. Hence, preventing osteolysis by tumor-activated osteoclasts and preventing development of skeletal metastasis may both be achieved by bisphosphonates but may require quite different chemical structures. —SF

Clinical Studies and Drug Effects

Lindsay R, Miller P, Pohl G, Glass EV, Chen P, Krege JH. Relationship between duration of teriparatide therapy and clinical outcomes in postmenopausal women with osteoporosis. *Osteoporos Int*. 2008 Oct 16; [Epub ahead of print] [Abstract]

Few data are available to determine whether any treatment reduces the absolute risk for fracture – i.e., that fracture rates during treatment in year 3 or beyond are lower than in the first or second year of treatment. Nor is it clear whether the relative risk reduction is maintained (in which case the absolute risk for fracture can go up or down but to different degrees in the groups). In about 1500 women receiving placebo or teriparatide 20 mg or 40 mg, risk for nonvertebral fractures and/or backpain decreased with time. The data suggest that the apparent rising risk for fracture is prevented, producing stable risk reduction, but it is not clear whether fracture rates in the latter months were actually lower than in earlier months; this would be consistent with reversal of fragility. —ES

Yao W, Cheng Z, Pham A, Busse C, Zimmermann EA, Ritchie RO, Lane NE. Glucocorticoid-induced bone loss in mice can be reversed by the actions of parathyroid hormone and risedronate on different pathways for bone formation and mineralization. *Arthritis Rheum*. 2008 Nov;58(11):3485-97. [Abstract]

> *Recent data indicate that intermittent PTH has greater effects on BMD and fractures compared to alendronate in glucocorticoid-induced osteoporosis. However, the mechanisms by which these drugs improve BMD and bone strength in response to corticosteroids remain poorly understood. This study uses a rodent model of bone loss and alteration of microstructure induced by prednisolone to unravel the tissue and molecular effects of PTH and risedronate treatment therein. Results indicate that both drugs improve bone mass, degree of bone mineralization, and bone strength in glucocorticoid-treated mice. PTH increases bone formation while risedronate reverses the deterioration of bone mineralization.* —SF

Genetics

Hennies HC, Kornak U, Zhang H, Egerer J, Zhang X, Seifert W, Kühnisch J, Budde B, Nätebus M, Brancati F, Wilcox WR, Müller D, Kaplan PB, Rajab A, Zampino G, Fodale V, Dallapiccola B, Newman W, Metcalfe K, Clayton-Smith J, Tassabehji M, Steinmann B, Barr FA, Nürnberg P, Wieacker P, Mundlos S. Gerodermia osteodysplastica is caused by mutations in SCYL1BP1, a Rab-6 interacting golgin. *Nat Genet*. 2008 Nov 9; [Epub ahead of print] [Abstract]

> *Gerodermia osteodysplastica (OMIM 231070) is a rare recessive progeria-like disorder of prematurely aged skin and severe osteoporosis. By performing a genome-wide linkage scan in 13 affected families of Mennonite origin, this study identifies a locus on 1q24 and subsequently a number of mutations in a gene that codes for a Golgi protein that is a partner of Rab6 and is thus involved in vesicular trafficking. How these gene mutations lead to osteoporosis and skin aging, however, remains to be fully elucidated, as does the potential role of this protein in common osteoporosis.* —SF

Ichikawa S, Koller DL, Curry LR, Lai D, Xuei X, Pugh EW, Tsai YY, Doheny KF, Edenberg HJ, Hui SL, Foroud T, Peacock M, Econs MJ. Identification of a linkage disequilibrium block in chromosome 1q associated with BMD in premenopausal white women. *J Bone Miner Res*. 2008 Oct;23(10):1680-8. [Abstract]

> *Peak BMD obtained during young adulthood is a major determinant of osteoporotic fractures. This paper describes a fine-mapping study for chromosome 1q, which showed significant linkage (LOD = 4.3) with variation in spinal areal BMD in healthy premenopausal white women in a previously reported study by the same group. Through a two-step strategy, this resarch demonstrates that genetic factor(s) in a 230-kb LD block in chromosome 1q play an important role in peak spinal BMD in healthy premenopausal white women.* —HWD

Kaufman JM, Ostertag A, Saint-Pierre A, Cohen-Solal M, Boland A, Van Pottelbergh I, Toye K, de Vernejoul MC, Martinez M. Genome-wide linkage screen of bone mineral density (BMD) in European pedigrees ascertained through a male relative with low BMD values: evidence for quantitative trait loci on 17q21-23, 11q12-13, 13q12-14, and 22q11. *J Clin Endocrinol Metab*. 2008 Oct;93(10):3755-62. [Abstract] [Full Text]

> *An autosomal genome-wide scan for BMD at the lumbar spine and femoral neck was conducted in a total of 103 pedigrees ascertained through a male relative with low BMD values at either the lumbar spine or femoral neck. The identified genomic regions largely overlapped with previous reported ones important to BMD or other bone-related traits.*

These regions also encompass several putative genes for osteoporosis such as COL1A1, SOST, and LRP5. —HWD

Napoli N, Rini GB, Serber D, Giri T, Yarramaneni J, Bucchieri S, Camarda L, Di Fede G, Camarda MR, Jain S, Mumm S, Armamento-Villareal R. The Val432Leu polymorphism of the CYP1B1 gene is associated with differences in estrogen metabolism and bone density. *Bone*. 2008 Oct 15; [Epub ahead of print] [Abstract]

Polymorphisms of the CYP1B1 gene, a member of the CYP450 superfamily, were tested for association with estrogen metabolism and BMD in 468 postmenopausal Caucasian women. The authors' findings suggest that through its effect on the rate of estrogen catabolism, the Val432Leu polymorphism of the CYP1B1 gene represents a possible genetic risk factor for osteoporosis in American women. —HWD

Yang TL, Chen XD, Guo Y, Lei SF, Wang JT, Zhou Q, Pan F, Chen Y, Zhang ZX, Dong SS, Xu XH, Yan H, Liu X, Qiu C, Zhu XZ, Chen T, Li M, Zhang H, Zhang L, Drees BM, Hamilton JJ, Papasian CJ, Recker RR, Song XP, Cheng J, Deng HW. Genome-wide copy-number-variation study identified a susceptibility gene, UGT2B17, for osteoporosis. *Am J Hum Genet*. 2008 Nov 5; [Epub ahead of print] [Abstract]

Recent genome-wide association studies (GWAS) for osteoporosis have focused on single nucleotide polymorphisms (SNPs) associated with BMD and/or fracture. However, a substantial proportion of genetic variation is represented by copy-number variation (CNV) (see review below by Altshuler and colleagues). In this GWAS for hip fractures vs controls in Chinese individuals, the authors extracted information on CNVs from the Affymetrix 500k gene chip, found association of some CNVs with fracture risk and then identified a deletion variant in the gene UGT2B17, encoding an enzyme for steroid metabolism. As with all good association studies, the findings were replicated in an independent cohort of Chinese individuals with and without hip fractures. —SF

Molecular and Cell Biology

Case N, Ma M, Sen B, Xie Z, Gross TS, Rubin J. Beta-catenin levels influence rapid mechanical responses in osteoblasts. *J Biol Chem*. 2008 Oct 24;283(43):29196-205. [Abstract] [Full Text]

Biomechanical stimulation of bone formation is now known to be at least partly mediated by an inhibition of sclerostin and to engage the Wnt/LRP5/β-catenin pathway. This in vitro work on osteoblasts indicates that strain may directly induce translocation of β-catenin to the nucleus, i.e., act downstream of the receptor complex. —SF

Hurtel AS, Mentaverri R, Caudrillier A, Cournarie F, Wattel A, Kamel S, Terwilliger EF, Brown EM, Brazier M. The calcium-sensing receptor is involved in strontium ranelate-induced osteoclast apoptosis: New insights into the associated signalling pathways. *J Biol Chem*. 2008 Oct 16; [Epub ahead of print]

Strontium (Sr^{2+}_o) dose-dependently stimulates the apoptosis of mature osteoclasts through the Ca^{2+}_o-sensing receptor (CaR), which results in stimulation of a PLC-dependent signaling pathway and nuclear translocation of NF-kB. Unlike Ca^{2+}_o, Sr^{2+}_o-induced osteoclast apoptosis depends on PKCII activation and is independent of IP3 action. Sr^{2+}_o and Ca^{2+}_o in combination exert a greater effect on apoptosis than either by itself. —ES

Masuyama R, Vriens J, Voets T, Karashima Y, Owsianik G, Vennekens R, Lieben L, Torrekens S, Moermans K, Vanden Bosch A, Bouillon R, Nilius B, Carmeliet G. TRPV4-mediated calcium influx regulates terminal differentiation of osteoclasts. *Cell Metab*. 2008 Sept;8(3):257-65. [Abstract]

> *The authors demonstrate that genetic ablation of TRPV4, a Ca^{2+}-permeable channel of the TRP family, increases bone mass by impairing bone resorption in mice. TRPV4 mediates basolateral Ca^{2+} influx specifically in large osteoclasts when Ca^{2+} oscillations decline. Thus, TRPV4-mediated Ca^{2+} influx secures intracellular Ca^{2+} concentrations to ensure NFATc1-regulated gene transcription, and regulates the terminal differentiation and activity of osteoclasts. TRPV4 can become a therapeutic target for bone diseases.* —TM

Sanchez-Fernandez MA, Gallois A, Riedl T, Jurdic P, Hoflack B. Osteoclasts control osteoblast chemotaxis via PDGF-BB/PDGF receptor beta signaling. *PLoS ONE*. 2008;3(10):e3537. [Abstract]

> *The mediators of osteoblast recruitment by osteoclasts are still poorly known. Platelet-derived growth factor (PDGF) has been suggested to be one of them. Using Boyden co-culture chambers, this study further shows that RANKL-differentiated osteoclasts producing PDGF-bb stimulate recruitment of osteoblast precursors in vitro and that either inhibition of PDGF gene expression in osteoclasts or the PDGF receptor gene in osteoblasts reduces chemoattraction of osteoblasts by osteoclasts.* —SF

Matsubara T, Kida K, Yamaguchi A, Hata K, Ichida F, Meguro H, Aburatani H, Nishimura R, Yoneda T. BMP2 regulates Osterix through Msx2 and Runx2 during osteoblast differentiation. *J Biol Chem*. 2008 Oct 24;283(43):29119-25. [Abstract] [Full Text]

> *BMP2 induced Msx2 and Osterix expression and promoted osteoblastic differentiation in mesenchymal cells from Runx2-deficient mice. Overexpression of Smad1 and Smad4 up-regulated Osterix expression, and Smad6 suppressed BMP2-induced Osterix expression in Runx2-deficient cells. Overexpression of Msx2 enhanced and knockdown of Msx2 inhibited Osterix expression enhanced by BMP2 in Runx2-deficient cells. In addition, Osterix and Runx2 regulated the expression of distinct proteins. Thus, Osterix is regulated not only by Runx2-dependent but also Msx2-dependent mechanisms, and Osterix and Runx2 control osteoblast differentiation by regulating distinct gene expression.* —TM

Tominaga H, Maeda S, Hayashi M, Takeda S, Akira S, Komiya S, Nakamura T, Akiyama H, Imamura T. CCAAT/enhancer-binding protein beta promotes osteoblast differentiation by enhancing Runx2 activity with ATF4. *Mol Biol Cell*. 2008 Oct 8; [Epub ahead of print] [Abstract]

> *Deletion of the C/EBPβ gene from mice resulted in suppression of osteoblast differentiation and delayed bone formation with concurrent suppression of chondrocyte maturation. In osteoblasts, C/EBPβ heterodimerized with ATF4, and this complex transactivated OSE1 of the osteocalcin promoter. C/EBPβ also enhanced the synergistic effect of ATF4 and Runx2 on osteocalcin promoter transactivation by enhancing their interaction. These results provide evidence that C/EBPβ is a crucial co-factor in the promotion of osteoblast maturation by Runx2 and ATF4.* —TM

Wu JY, Purton LE, Rodda SJ, Chen M, Weinstein LS, McMahon AP, Scadden DT, Kronenberg HM. Osteoblastic regulation of B lymphopoiesis is mediated by Gsalpha-dependent signaling pathways. *Proc Natl Acad Sci U S A*. 2008 Nov 4;105(44):16976-81. [Abstract] [Full Text]

Osteoimmunology is not only about modulation of bone turnover by immune and inflammatory cells, but also about the importance of the bone niche for hematopoietic/immune cells. Here, deletion of Gsα (a subunit from the heterotrimeric G protein complex responsible for cAMP signaling) in osteoblast progenitors – using an Osterix promoter Cre – not only resulted in dramatically reduced osteoblast surfaces and low trabecular bone volume, but also in decreased numbers of B cells, whereas T cells were preserved. Low B cell numbers may be explained by a marked reduction of IL-7 expression by osteoblasts without cAMP signaling. —SF

Physiology and Metabolism

Asaba Y, Ito M, Fumoto T, Watanabe K, Fukuhara R, Takeshita S, Nimura Y, Ishida J, Fukamizu A, Ikeda K. Activation of renin-angiotensin system induces osteoporosis independently of hypertension. *J Bone Miner Res*. 2008 Oct 10; [Epub ahead of print] [Abstract]

Activation of the renin-angiotensin system (RAS) increases bone turnover. Transgenic mice expressing the human renin gene were normotensive and had a low bone mass. Angiotensin II (AngII) acted on osteoblasts and increased RANKL and VEGF, thus stimulating the formation of osteoclasts. Knockdown of the AT2 receptor inhibited AngII activity, while silencing of the AT1 receptor enhanced it, suggesting a functional interaction between the 2 AngII receptors on the osteoblastic cell surface. Finally, treatment of THM mice with an ACE inhibitor, enalapril, improved osteoporosis as well as hypertension, whereas treatment with losartan, an ARB specific for AT1, resulted in exacerbation of the low bone mass phenotype. —ES

Okazaki M, Ferrandon S, Vilardaga JP, Bouxsein ML, Potts JT Jr, Gardella TJ. Prolonged signaling at the parathyroid hormone receptor by peptide ligands targeted to a specific receptor conformation. *Proc Natl Acad Sci U S A*. 2008 Oct 28;105(43):16525-30. [Abstract] [Full Text]

Structure-function studies of PTH ligand and receptor have led here to the development of PTH analogs with prolonged binding and cAMP signaling in vitro. In vivo testing of these compounds indicates increased bone resorption, hypercalcemia and hypophosphatemia, together with improved trabecular bone volume. These results are similar to previous observations with a long-acting PTH-Fc fusion molecule, which therefore reinforces the new paradigm that bone anabolism by long-lasting PTH analogs can be obtained simultaneously with catabolism and hypercalcemia. —SF

Public Health

Rabenda V, Vanoverloop J, Fabri V, Mertens R, Sumkay F, Vannecke C, Deswaef A, Verpooten GA, Reginster JY. Low incidence of anti-osteoporosis treatment after hip fracture. *J Bone Joint Surg Am*. 2008 Oct;90(10):2142-8. [Abstract] [Full Text]

Of 23,146 patients who had a hip fracture, 6% received treatment. Bisphosphonate treatment was dispensed to 2.6% and 3.6% of the patients within six months and one year after the occurrence of the hip fracture, respectively. —ES

Reviews, Perspectives and Editorials

Altshuler D, Daly MJ, Lander ES. Genetic mapping in human disease. *Science*. 2008 Nov 7;322(5903):881-8. [Abstract] [Full Text]

Díez-Pérez A, González-Macías J. Inadequate responders to osteoporosis treatment: proposal for an operational definition. *Osteoporos Int*. 2008 Nov;19(11):1511-6. [Abstract]

Segovia-Silvestre T, Neutzsky-Wulff AV, Sorensen MG, Christiansen C, Bollerslev J, Karsdal MA, Henriksen K. Advances in osteoclast biology resulting from the study of osteopetrotic mutations. *Hum Genet*. 2008 Nov 6; [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Allison S, Baldock P, Enriquez R, Lin E, During M, Gardiner E, Eisman J, Sainsbury A, Herzog H. Critical interplay between neuropeptide Y and sex steroid pathways in bone and adipose tissue homeostasis. *J Bone Miner Res*. 2008 Oct 10; [Epub ahead of print] [Abstract]

Diao H, Iwabuchi K, Li L, Onoe K, Van Kaer L, Kon S, Saito Y, Morimoto J, Denhardt DT, Rittling S, Uede T. Osteopontin regulates development and function of invariant natural killer T cells. *Proc Natl Acad Sci U S A*. 2008 Oct 14;105(41):15884-9. [Abstract] [Full Text]

Fukunaga E, Inoue Y, Komiya S, Horiguchi K, Goto K, Saitoh M, Miyazawa K, Koinuma D, Hanyu A, Imamura T. Smurf2 induces ubiquitin-dependent degradation of Smurf1 to prevent migration of breast cancer cells. *J Biol Chem*. 2008 Oct 16; [Epub ahead of print]

Hikata T, Takaishi H, Takito J, Hakozaki A, Furukawa M, Uchikawa S, Kimura T, Okada Y, Matsumoto M, Yoshimura A, Nishimura R, Reddy SV, Asahara H, Toyama Y. PIAS3 negatively regulates RANKL-mediated osteoclastogenesis directly in osteoclast precursors and indirectly via osteoblasts. *Blood*. 2008 Oct 24; [Epub ahead of print]

Izu Y, Mizoguchi F, Kawamata A, Hayata T, Nakamoto T, Nakashima K, Inagami T, Ezura Y, Noda M. Angiotensin II type 2 receptor blockade increases bone mass. *J Biol Chem*. 2008 Nov 11; [Epub ahead of print]

Karasik D, Shimabuku NA, Zhou Y, Zhang Y, Cupples LA, Kiel DP, Demissie S. A genome wide linkage scan of metacarpal size and geometry in the Framingham Study. *Am J Hum Biol*. 2008 Nov-Dec;20(6):663-70. [Abstract]

Kärner E, Unger C, Cerny R, Ahrlund-Richter L, Ganss B, Dilber MS, Wendel M. Differentiation of human embryonic stem cells into osteogenic or hematopoietic lineages: A dose-dependent effect of osterix over-expression. *J Cell Physiol*. 2008 Oct 17;218(2):323-33. [Abstract]

Kartsogiannis V, Sims NA, Quinn JM, Ly C, Cipetic M, Poulton IJ, Walker EC, Saleh H, McGregor NE, Wallace ME, Smyth MJ, Martin TJ, Zhou H, Ng KW, Gillespie MT. Osteoclast inhibitory lectin, an immune cell product that is required for normal bone physiology in vivo. *J Biol Chem*. 2008 Nov 7;283(45):30850-60. [Abstract] [Full Text]

Khatri R, Schipani E. About the importance of being desulfated. *Genes Dev*. 2008 Oct 15;22(20):2750-4. [Abstract]

Lau AN, Ali SH, Sawka AM, Thabane L, Papaioannou A, Gafni A, Adachi JD. Improvement in health-related quality of life in osteoporosis patients treated with teriparatide. *BMC Musculoskelet Disord*. 2008 Nov 7;9(1):151. [Abstract]

Lewis J. From signals to patterns: space, time, and mathematics in developmental biology. *Science*. 2008 Oct 17;322(5900):399-403. [Abstract] [Full Text]

Lippuner K, Johansson H, Kanis JA, Rizzoli R. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. *Osteoporos Int*. 2008 Oct 31; [Epub ahead of print] [Abstract]

Mori H, Tanaka M, Kayasuga R, Masuda T, Ochi Y, Yamada H, Kishikawa K, Ito M, Nakamura T. Minodronic acid (ONO-5920/YM529) prevents decrease in bone mineral density and bone strength, and improves bone microarchitecture in ovariectomized cynomolgus monkeys. *Bone*. 2008 Nov;43(5):840-8. [Abstract]

Motyl KJ, McCabe LR. Leptin treatment prevents type I diabetic marrow adiposity but not bone loss in mice. *J Cell Physiol*. 2008 Oct 17; [Epub ahead of print] [Abstract]

Olivares-Navarrete R, Raz P, Zhao G, Chen J, Wieland M, Cochran DL, Chaudhri RA, Ornoy A, Boyan BD, Schwartz Z. Integrin alpha2beta1 plays a critical role in osteoblast response to micron-scale surface structure and surface energy of titanium substrates. *Proc Natl Acad Sci U S A*. 2008 Oct 14;105(41):15767-72. [Abstract] [Full Text]

Recker RR, Bare SP, Smith SY, Varela A, Miller MA, Morris SA, Fox J. Cancellous and cortical bone architecture and turnover at the iliac crest of postmenopausal osteoporotic women treated with parathyroid hormone 1-84. *Bone*. 2008 Oct 17; [Epub ahead of print] [Abstract]

Viegas CS, Simes DC, Laize V, Williamson MK, Price PA, Cancela ML. GLA-rich protein (GRP): A new vitamin K-dependent protein identified from sturgeon cartilage and highly conserved in vertebrates. *J Biol Chem*. 2008 Oct 3; [Epub ahead of print]

von Marschall Z, Fisher LW. Dentin matrix protein-1 isoforms promote differential cell attachment and migration. *J Biol Chem*. 2008 Nov 21;283(47):32730-40. [Abstract] [Full Text]

Wu S, Fadoju D, Rezvani G, De Luca F. The stimulatory effects of insulin-like growth factor-1 on growth plate chondrogenesis are mediated by nuclear factor-kB p65. *J Biol Chem*. 2008 Oct 15; [Epub ahead of print]

Xu K, Nowak I, Kirchner M, Xu Y. Recombinant collagen studies link the severe conformational changes induced by osteogenesis imperfecta mutations to the disruption of a set of interchain salt-bridges. *J Biol Chem*. 2008 Oct 8; [Epub ahead of print]

Yano A, Tsutsumi S, Soga S, Lee MJ, Trepel J, Osada H, Neckers L. Inhibition of Hsp90 activates osteoclast c-Src signaling and promotes growth of prostate carcinoma cells in bone. *Proc Natl Acad Sci U S A*. 2008 Oct 7;105(40):15541-6. [Abstract] [Full Text]

Zhang Z, Zhang Y, Ning G, Deb DK, Kong J, Li YC. Combination therapy with AT1 blocker and vitamin D analog markedly ameliorates diabetic nephropathy: blockade of compensatory renin increase. *Proc Natl Acad Sci U S A*. 2008 Oct 14;105(41):15896-901. [Abstract] [Full Text]

Zhu S, Barbe MF, Liu C, Hadjiargyrou M, Popoff SN, Rani S, Safadi FF, Litvin J. Periostin-like-factor in osteogenesis. *J Cell Physiol*. 2008 Nov 12; [Epub ahead of print] [Abstract]

Zlowodzki M, Brink O, Switzer J, Wingerter S, Woodall J Jr, Petrisor BA, Kregor PJ, Bruinsma DR, Bhandari M. The effect of shortening and varus collapse of the femoral neck on function after fixation of intracapsular fracture of the hip: a multi-centre cohort study. *J Bone Joint Surg Br*. 2008 Nov;90(11):1487-94. [Abstract]

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.