

## **NOT TO BE MISSED**

### **Clinical and Basic Research Papers – June 2011**

**Serge Ferrari, Editor-in-Chief**  
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#### **Highlighted Paper**

◆ Cui Y, Niziolek PJ, Macdonald BT, Zylstra CR, Alenina N, Robinson DR, Zhong Z, Matthes S, Jacobsen CM, Conlon RA, Brommage R, Liu Q, Mseeh F, Powell DR, Yang QM, Zambrowicz B, Gerrits H, Gossen JA, He X, Bader M, Williams BO, Warman ML, Robling AG. Lrp5 functions in bone to regulate bone mass. *Nat Med*. 2011 Jun;17(6):684-91. [\[Abstract\]](#)

◆ Bonewald L. The holy grail of high bone mass. *Nat Med*. 2011 Jun;17(6):657-8. [\[Info\]](#)

*It took several years and a huge collective effort to eventually demonstrate that LRP5-mediated regulation of bone mass takes place directly in bone cells, that is, not in the gut nor through serotonin. Osteocyte-targeted expression of LRP5 human mutations indeed influenced bone formation in mice. Moreover, limb-specific expression of LRP5 mutants affected limb bone mass, and not vertebrae, precluding a systemic effect. In contrast, expression of LRP5 mutants in the intestine did not affect serotonin levels nor bone. Serotonin antagonists had no effects on bone mass. Don't miss the 23 pages of supplemental data, which illustrate a real tour de force in experimental biology, nor the accompanying editorial. —SF*

**Considering the debate that these results are generating in the bone community, we encourage you to share your thoughts and comments on BoneKEy using this link:**

<http://www.bonekey-ibms.org/cgi/eletter-submit/ibmske;8/6/257>

#### **Clinical Studies and Drug Effects**

◆ Ma YL, Marin F, Stepan J, Ish-Shalom S, Mörnicke R, Hawkins F, Kapetanios G, de la Peña MP, Kekow J, Martínez G, Malouf J, Zeng QQ, Wan X, Recker RR. Comparative effects of teriparatide and strontium ranelate in the periosteum of iliac crest biopsies in postmenopausal women with osteoporosis. *Bone*. 2011 May 1;48(5):972-8. [\[Abstract\]](#)

*Tetracycline-labeled transiliac crest bone biopsies were analyzed from 27 patients receiving teriparatide (TPTD, 20µg/day) and 22 patients receiving strontium ranelate (SrR, 2g/day) after six months of treatment. At the combined periosteal cortex, the mineralization surface as a percent of bone surface (MS/BS%) was greater for TPTD (mean ± SE: 8.08 ± 1.22%) than SrR (3.22 ± 1.05%) (p < 0.005). The difference in mineral apposition rate (MAR) between TPTD (0.35 ± 0.06 µm/day) and SrR (0.14 ± 0.06 µm/day) was also significant (p < 0.05), while that of bone formation rate per bone*

surface (BFR/BS) between TPTD ( $0.014 \pm 0.004 \text{ mm}^3/\text{mm}^2/\text{year}$ ) and SrR ( $0.004 \pm 0.003 \text{ mm}^3/\text{mm}^2/\text{year}$ ) was not ( $p = 0.057$ ). Significant differences between the two treatments were also observed for MS/BS%, BFR/BS, MAR and the double-labeled perimeter in the periosteum of the thicker, but not thinner cortices. While most of the bone formation and mineralization variables were higher for TPTD- than SrR-treated women at both the periosteal and endosteal combined cortices, the data are difficult to interpret; there is placebo arm and there are no baseline values. —ES

- ◆ Pollock NK, Bernard PJ, Gower BA, Gundberg CM, Wenger K, Misra S, Bassali RW, Davis CL. Lower uncarboxylated osteocalcin concentrations in children with prediabetes is associated with beta-cell function. *J Clin Endocrinol Metab.* 2011 Apr 20. [Epub ahead of print] [\[Abstract\]](#)

In 140 overweight prepubertal children (43% female, 46% black, 84% obese) with normal glucose levels ( $n = 99$ ) and prediabetes ( $n = 41$ ), lower uncarboxylated osteocalcin, Matsuda index, insulinogenic index, and oral glucose tolerance test derived insulinogenic index and disposition index (DI(OGTT)) and higher visceral adipose tissue (VAT) levels were found in the prediabetes vs. normal-glucose group (all  $P < 0.03$ ). Carboxylated osteocalcin levels were not different between groups. Uncarboxylated osteocalcin was associated with insulinogenic index and DI(OGTT) ( $\beta = 0.34, 0.36$ , respectively, both  $P < 0.04$ ) in the prediabetes group but not the normal-glucose group. In both the normal-glucose and prediabetes groups, carboxylated osteocalcin was associated with insulin sensitivity ( $\beta = 0.26, 0.47$ , respectively, both  $P < 0.02$ ). Lower uncarboxylated osteocalcin concentrations in children with prediabetes may be associated with  $\beta$ -cell dysfunction. —ES

- ◆ Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med.* 2011 May 5;364(18):1728-37. [\[Abstract\]](#)

Among 1234 radiographs, 59 patients with atypical fractures were compared with 263 controls with ordinary subtrochanteric or shaft fractures. The age-adjusted relative risk of atypical fracture was 47.3 (95% CI, 25.6 to 87.3) but the increase in absolute risk was 5 per 10,000 patient-years. A total of 78% of the cases and 10% of the controls had received bisphosphonates, corresponding to an odds ratio (OR) of 33.3 (95% CI, 14.3 to 77.8). The duration of use influenced the risk (OR per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6). After drug withdrawal, the risk diminished by 70% per year since the last use (OR, 0.28; 95% CI, 0.21 to 0.38). —ES

## Cancer and Bone

- ◆ Liu S, Liu WT, Liu YP, Dong HL, Henkemeyer M, Xiong LZ, Song XJ. Blocking EphB1 receptor forward signaling in spinal cord relieves bone cancer pain and rescues analgesic effect of morphine treatment in rodents. *Cancer Res.* 2011 May 9. [Epub ahead of print] [\[Abstract\]](#)

- ◆ Hansen RR, Nielsen CK, Nasser A, Thomsen SI, Eghorn LF, Pham Y, Schulenburg C, Syberg S, Ding M, Stojilkovic SS, Jorgensen NR, Heegaard AM. P2X7 receptor-deficient mice are susceptible to bone cancer pain. *Pain.* 2011 May 10. [Epub ahead of print] [\[Abstract\]](#)

Treating bone cancer pain continues to be a clinical challenge and underlying mechanisms of bone cancer pain remain elusive. These 2 papers report on the roles of EphB1 and P2X7 receptors in bone cancer pain. In the first paper, Liu and colleagues have shown that the intratibial implantation of Walker-256 rat mammary carcinoma cells leads to pain behaviors and bone destruction that are associated with the upregulation of EphB1 receptor and its ligand ephrinB2 in the dorsal horn and primary

*sensory neurons. In addition, spinal administration of an EphB1 receptor blocking reagent EphB2-Fc prevents and reverses bone cancer pain behaviors by downregulating EphB1 and increasing activity of matrix metalloproteinase (MMP)-2/9, which cleaves EphB receptors. These findings suggest a potential target for treating bone cancer pain.*

*The purinergic P2X7 receptor has been implicated previously in both neuropathic and inflammatory pain. In the second paper, Hansen and colleagues have investigated the role of the P2X7 receptor in bone cancer pain. The authors demonstrated that P2X7 receptor knockout (P2X7R KO) mice were susceptible to bone cancer pain, and that a selective P2X7 receptor antagonist failed to alleviate pain-related behaviors in models of bone cancer pain induced by 4T1 mammary cancer cells or NCTC 2472 osteosarcoma cells. These results suggest that P2X7 receptors play a negligible role in bone cancer pain. —PC*

- ◆ Mehra R, Kumar-Sinha C, Lonigro RJ, Shankar S, Jing X, Phillips NE, Han B, Cao X, Smith DC, Shah RB, Chinnaiyan AM, Pienta KJ. Characterization of bone metastases from rapid autopsies of prostate cancer patients. *Clin Cancer Res.* 2011 May 9. [Epub ahead of print] [\[Abstract\]](#)

*Bone is the most common metastatic site for prostate cancer, and osseous metastases are the leading cause of morbidity from this disease. Mehra and colleagues report a reproducible methodology to obtain high quality clinical tumor tissues metastatic to bone. Gene expression profiling data from five soft bone-metastatic cancer prostate tissues compared with patient-matched non-osseous metastatic cancer tissues revealed 672 probes, corresponding to 664 unique genes, differentially expressed in lethal bone-metastatic tissues. This study provides leads towards a better understanding of the steps in metastasis and the phenotypic characteristics of osseous metastasis of prostate cancer. —PC*

- ◆ Su Y, Wagner ER, Luo Q, Huang J, Chen L, He BC, Zuo GW, Shi Q, Zhang BQ, Zhu G, Bi Y, Luo J, Luo X, Kim SH, Shen J, Rastegar F, Huang E, Gao Y, Gao JL, Yang K, Wietholt C, Li M, Qin J, Haydon RC, He TC, Luu HH. Insulin-like growth factor binding protein 5 suppresses tumor growth and metastasis of human osteosarcoma. *Oncogene.* 2011 Apr 4. [Epub ahead of print] [\[Abstract\]](#)

*In this study, Su and colleagues identified insulin-like growth factor binding protein 5 (IGFBP5) as being significantly downregulated in a highly metastatic osteosarcoma subline derived from the less metastatic human MG63 line. In an orthotopic xenograft animal model, overexpression of IGFBP5 inhibited osteosarcoma tumor growth and pulmonary metastases. Conversely, siRNA-mediated knockdown of IGFBP5 promoted osteosarcoma tumor growth and pulmonary metastases in vivo. Immunohistochemical staining of patient-matched primary and metastatic osteosarcoma samples demonstrated decreased IGFBP5 expression in the metastases. Thus, IGFBP5 may contribute to the development of osteosarcoma metastasis. —PC*

- ◆ Xing F, Okuda H, Watabe M, Kobayashi A, Pai SK, Liu W, Pandey PR, Fukuda K, Hirota S, Sugai T, Wakabayashi G, Koeda K, Kashiwaba M, Suzuki K, Chiba T, Endo M, Mo YY, Watabe K. Hypoxia-induced Jagged2 promotes breast cancer metastasis and self-renewal of cancer stem-like cells. *Oncogene.* 2011 Apr 18. [Epub ahead of print] [\[Abstract\]](#)

*Notch signaling is often and aberrantly activated by hypoxia during tumor progression. It has been demonstrated recently that Jagged1 promotes breast cancer bone metastasis by engaging Notch signaling in osteoblasts and osteoclasts ([Sethi et al. Cancer Cell. 2011 Feb 15;19\(2\):192-205](#)). In this study, Xing and colleagues found that*

*the expression of Jagged2 is significantly correlated with the overall- and metastasis-free survival of breast cancer patients and, as judged by immunohistochemistry, both Jagged2 and Notch signaling were strongly upregulated at the hypoxic invasive front of breast tumor tissue. Importantly, Jagged2 was also found to be upregulated in bone marrow stroma under hypoxia and promoted the growth of cancer stem-like cells by activating their Notch signaling. —PC*

## Genetics

◆Albagha OM, Wani SE, Visconti MR, Alonso N, Goodman K, Brandi ML, Cundy T, Chung PY, Dargie R, Devogelaer JP, Falchetti A, Fraser WD, Gennari L, Gianfrancesco F, Hooper MJ, Van Hul W, Isaia G, Nicholson GC, Nuti R, Papapoulos S, Montes JD, Ratajczak T, Rea SL, Rendina D, Gonzalez-Sarmiento R, Di Stefano M, Ward LC, Walsh JP, Ralston SH for the Genetic Determinants of Paget's Disease (GDPD) Consortium. Genome-wide association identifies three new susceptibility loci for Paget's disease of bone. *Nat Genet.* 2011 May 29. [Epub ahead of print] [\[Abstract\]](#)

*This is the second GWAS of Paget's disease of bone (PDB). The only known mutated gene causing PDB was SQSTM1, which encodes the protein sequestosome-1/p62. Therefore this GWAS excluded PDB cases with any SQSTM1 mutations. In the first GWAS ([Albagha et al. Nat Genet. 2010 Jun;42\(6\):520-4](#)), using a large sample of PDB cases and controls, the authors discovered (and then replicated in an independent set) four top genes: CSF1 on chromosome 1p13, which encodes macrophage colony-stimulating factor (M-CSF); OPTN on 10p13, which encodes optineurin; TNFRSF11A on 18q21, which encodes RANK; and TM7SF4 on 8q22, which encodes DC-STAMP. The new associations in this recent paper are with PML on 15q24; RIN3 on 14q32; and NUP205 on 7q33. Together, these seven loci explained ~13% of the familial risk of PDB. —DK*

◆Katz J, Gong Y, Salmasinia D, Hou W, Burkley B, Ferreira P, Casanova O, Langaee TY, Moreb JS. Genetic polymorphisms and other risk factors associated with bisphosphonate induced osteonecrosis of the jaw. *Int J Oral Maxillofac Surg.* 2011 Jun;40(6):605-11. [\[Abstract\]](#)

*Bisphosphonate-induced osteonecrosis of the jaw (BONJ) is a complication in patients taking bisphosphonates. In this study, patients with multiple myeloma on intravenous bisphosphonate therapy were enrolled; of the 78 patients enrolled, 12 had BONJ. The authors revealed a significant association between BONJ and smoking ( $p = 0.048$ ) and type of BP treatment ( $p = 0.03$ ). They also tested 10 SNPs from seven candidate genes. A trend for higher odds for BONJ was found for SNPs in five genes: COL1A1, RANK, MMP2, OPG, and OPN. A genetic score of all five SNPs together was a strong independent risk factor for BONJ, with an adjusted odds ratio of 11.2 (95% CI, 1.8-69.9;  $p = 0.0097$ ). —DK*

◆Kou I, Takahashi A, Urano T, Fukui N, Ito H, Ozaki K, Tanaka T, Hosoi T, Shiraki M, Inoue S, Nakamura Y, Kamatani N, Kubo M, Mori S, Ikegawa S. Common variants in a novel gene, FONG on chromosome 2q33.1 confer risk of osteoporosis in Japanese. *PLoS ONE.* 2011 May 6;6(5):e19641. [\[Abstract\]](#)

*This group conducted a GWAS in Japanese cases (postmenopausal women over 60 years of age) and controls (from the BioBank Japan Project). Despite rather sparse SNP coverage (268,064 Perlegen SNPs were genotyped and 224,507 passed QC filters), the authors identified a SNP associated with osteoporosis (combined  $P = 1.51 \times 10^{-8}$ , odds ratio = 1.25), in a previously unknown gene – FONG, which consists*

*of 4 exons. FONG is predicted to encode a 147 amino acid protein, which is ubiquitously expressed in various tissues, mostly in skeletal muscle, the liver, and also bone; its function is still unknown. —DK*

## **Bone Modeling, Remodeling, and Repair**

- ◆Coleman CM, Scheremeta BH, Boyce AT, Mauck RL, Tuan RS. Delayed fracture healing in growth differentiation factor 5-deficient mice: a pilot study. *Clin Orthop Relat Res.* 2011 May 18. [Epub ahead of print] [\[Abstract\]](#)

*The absence of GDF-5 impaired cartilaginous matrix deposition in the callus and reduced callus cross-sectional area. After 56 days, the repaired fracture was mechanically comparable to that of controls. Although GDF-5 deficiency did not compromise long-term fracture healing, a delay in cartilage formation and remodeling supports roles for GDF-5 in the early phase of bone repair. The authors conclude that local delivery of GDF-5 to clinically difficult fractures may simulate cartilage formation in the callus and support subsequent remodeling. —DGL*

- ◆Dong XN, Qin A, Xu J, Wang X. In situ accumulation of advanced glycation endproducts (AGEs) in bone matrix and its correlation with osteoclastic bone resorption. *Bone.* 2011 Apr 21. [Epub ahead of print] [\[Abstract\]](#)

*Advanced glycation end products (AGEs) accumulate in bone with increasing age. Human cortical bone specimens from young ( $31 \pm 6$  years of age), middle-aged ( $51 \pm 3$  years of age) and elderly ( $76 \pm 4$  years of age) groups were examined. The greatest amount of AGEs was found in the interstitial tissue, followed by old osteons, and the least in newly-formed osteons, suggesting that the younger the donor the less AGEs were accumulated in the tissue. AGE accumulation appeared to initiate from the region of cement lines, and spread to the other parts as the tissue aged. Bone resorption activities of osteoclasts were positively correlated with the in situ concentration of AGEs and such an effect was enhanced with increasing age. —ES*

- ◆Kidd LJ, Cowling NR, Wu AC, Kelly WL, Forwood MR. Bisphosphonate treatment delays stress fracture remodeling in the rat ulna. *J Orthop Res.* 2011 May 19. [Epub ahead of print] [\[Abstract\]](#)

*High-dose bisphosphonate treatment impaired healing of a large stress fracture line by reducing the volume of bone resorbed and replaced during remodeling. However, periosteal callus formation was not adversely affected by risedronate treatment. Further evidence that BPs affect remodeling but not modeling. —DGL*

## **Molecular and Cell Biology**

- ◆Chim SM, Qin A, Tickner J, Pavlos N, Davey T, Wang H, Guo Y, Zheng MH, Xu J. EGFL6 promotes endothelial cell migration and angiogenesis through the activation of ERK. *J Biol Chem.* 2011 Apr 29. [Epub ahead of print] [\[Abstract\]](#)

*EGFL6 induces angiogenesis by a paracrine mechanism. EGFL6 is expressed in osteoblastic-like cells but promotes migration and angiogenesis of endothelial cells. Conditioned medium containing EGFL6 potentiates SVEC endothelial cell migration and EGFL6 promotes endothelial cell tube-like structure formation in Matrigel assays and angiogenesis in a chick embryo chorioallantoic membrane. EGFL6 recombinant protein induces phosphorylation of ERK in SVEC endothelial cells. Inhibition of ERK impaired EGFL6-induced ERK activation and endothelial cell migration. EGFL6 mediates cross-talk between vascular endothelial cells and osteoblastic-like cells.*

—ES

- ◆de Gorter DJ, van Dinther M, Korchynskiy O, Ten Dijke P. Biphasic effects of transforming growth factor  $\beta$  on bone morphogenetic protein-induced osteoblast differentiation. *J Bone Miner Res.* 2011 Jun;26(6):1178-87. [[Abstract](#)]

*An understanding of TGF- $\beta$  effects on bone remains elusive, with many contradictory in vivo and in vitro studies. This paper may shed some light on the subject. The stimulatory and inhibitory effects of TGF- $\beta$  were found to depend on timing and duration of co-stimulation. TGF- $\beta$  inhibited BMP-induced activation of a BMP-Smad-dependent luciferase reporter, suggesting that the stimulatory effect of TGF- $\beta$  is not due to increased BMP-Smad activity. TGF- $\beta$  also inhibited the BMP-induced expression of the BMP antagonist noggin and prolonged BMP activity. TGF- $\beta$ , besides classically acting as an inhibitor of differentiation, can also dampen the noggin-mediated negative-feedback loop, thus enhancing BMP-induced osteoblast differentiation, which might be beneficial in fracture healing. —DGL*

- ◆Rybchyn MS, Slater M, Conigrave AD, Mason RS. An Akt-dependent increase in canonical Wnt signalling and a decrease in sclerostin protein levels are involved in strontium ranelate-induced osteogenic effects in human osteoblasts. *J Biol Chem.* 2011 May 12. [Epub ahead of print] [[Abstract](#)]

*Exposure of human osteoblasts in culture to strontium increased mineralization and decreased the expression of sclerostin, a negative regulator of bone formation that inhibits Wnt signaling. Strontium activated an Akt-dependent signaling cascade via the calcium-sensing receptor that promoted the nuclear translocation of  $\beta$ -catenin. While encouraging, the relevance of these in vitro observations is yet to be determined as in vivo evidence for an anabolic effect of strontium ranelate – the formation of new lamellar bone – is lacking. —ES*

## Physiology and Metabolism

- ◆Yoshikawa Y, Kode A, Xu L, Mosialou I, Silva BC, Ferron M, Clemens TL, Economides AN, Kousteni S. Genetic evidence points to an osteocalcin-independent influence of osteoblasts on energy metabolism. *J Bone Miner Res.* 2011 May 6. [Epub ahead of print] [[Abstract](#)]

*Ablation of osteoblasts in adult mice affected glucose metabolism. In a manner similar to what is seen in the case of osteocalcin deficiency, a partial ablation of this cell population resulted in hypoinsulinemia, hyperglycemia, glucose intolerance and decreased insulin sensitivity. However, and unlike what is seen in osteocalcin-deficient mice, osteoblast ablation also decreased gonadal fat, increased energy expenditure and the expression of resistin, an adipokine proposed to mediate insulin resistance. Administration of osteocalcin reversed, fully, the glucose intolerance and reinstated normal blood glucose and insulin levels, but it only partially restored insulin sensitivity and did not affect the improved gonadal fat weight and energy expenditure in osteoblast-depleted mice. —ES*

## Reviews, Perspectives and Editorials

- ◆Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: current concepts and future directions. *BMC Med.* 2011 May 31;9(1):66. [[Abstract](#)]

- ◆Takahata M, Awad HA, O'Keefe RJ, Bukata SV, Schwarz EM. Endogenous tissue engineering:

PTH therapy for skeletal repair. *Cell Tissue Res.* 2011 May 31. [Epub ahead of print] [\[Abstract\]](#)

### Other Studies of Potential Interest

◆Gomberg SJ, Wustrack RL, Napoli N, Arnaud CD, Black DM. Teriparatide, vitamin d, and calcium healed bilateral subtrochanteric stress fractures in a postmenopausal woman with a 13-year history of continuous alendronate therapy. *J Clin Endocrinol Metab.* 2011 Jun;96(6):1627-32. [\[Abstract\]](#) [\[Full Text\]](#)

◆Powe CE, Ricciardi C, Berg AH, Erdenesanaa D, Collerone G, Ankers E, Wenger J, Karumanchi SA, Thadhani R, Bhan I. Vitamin D binding protein modifies the vitamin D-bone mineral density relationship. *J Bone Miner Res.* 2011 Mar 17. [Epub ahead of print] [\[Abstract\]](#)

◆Puah KL, Tan MH. Bisphosphonate-associated atypical fracture of the femur: Spontaneous healing with drug holiday and re-appearance after resumed drug therapy with bilateral simultaneous displaced fractures - a case report. *Acta Orthop.* 2011 May;82(3):380-2. [\[Abstract\]](#)

◆Rule AD, de Andrade M, Matsumoto M, Mosley TH, Kardia S, Turner ST. Association between SLC2A9 transporter gene variants and uric acid phenotypes in African American and white families. *Rheumatology (Oxford).* 2011 May;50(5):871-8. [\[Abstract\]](#)

◆Szulc P, Hawa G, Boutroy S, Vilayphiou N, Schoppet M, Chapurlat R, Hofbauer LC. Cortical bone status is associated with serum osteoprotegerin concentration in men: the STRAMBO study. *J Clin Endocrinol Metab.* 2011 May 11. [Epub ahead of print] [\[Abstract\]](#)

◆Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, Napoli N, Qualls C, Shah K. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med.* 2011 Mar 31;364(13):1218-29. [\[Abstract\]](#)

◆Vissers LE, Lausch E, Unger S, Campos-Xavier AB, Gilissen C, Rossi A, Del Rosario M, Venselaar H, Knoll U, Nampoothiri S, Nair M, Spranger J, Brunner HG, Bonafé L, Veltman JA, Zabel B, Superti-Furga A. Chondrodysplasia and abnormal joint development associated with mutations in IMPAD1, encoding the golgi-resident nucleotide phosphatase, gPAPP. *Am J Hum Genet.* 2011 May 13;88(5):608-15. [\[Abstract\]](#)

◆Williams FM, Popham M, Sambrook PN, Jones AF, Spector TD, Macgregor AJ. Progression of lumbar disc degeneration over a decade: a heritability study. *Ann Rheum Dis.* 2011 Jul;70(7):1203-7. [\[Abstract\]](#)

**Conflict of Interest:** Dr. Clézardin reports receiving research support from Novartis (Basel, Switzerland) and honoraria for advisory work and speaking engagements from Novartis and Amgen. Dr. Ferrari reports that he receives research support from Amgen and Merck Sharp & Dohme, and is an advisory committee member and lectures occasionally at conference symposia for the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Merck Sharp & Dohme, Eli Lilly, Servier, and Novartis. 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 reports that he is a member of the advisory board for Eli Lilly, and receives consultancy fees from Chugai, Astellas, Teijin, JT, and Daiichi-Sankyo. Dr. Karasik reports no conflicts of interest.