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NOT TO BE MISSED

Clinical and Basic Research Papers – February 2009

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Bone Modeling, Remodeling and Repair

Cardoso L, Herman BC, Verborgt O, Laudier D, Majeska RJ, Schaffler MB. Osteocyte apoptosis controls activation of intracortical resorption in response to bone fatigue. *J Bone Miner Res*. 2008 Dec 2. [Epub ahead of print] [Abstract]

> *Osteocyte apoptosis is an important early step in the activation and targeting of osteoclastic resorption after fatigue damage. Osteocytes surrounding microcracks undergo apoptosis and co-localize with areas resorbed by osteoclasts. A pan-caspase inhibitor blocked fatigue-induced apoptosis and the activation of osteoclastic resorption.* —ES

Chen Y, Alman BA. Wnt pathway, an essential role in bone regeneration. *J Cell Biochem*. 2009 Jan 6;106(3):353-362. [Abstract]

> *A nice summary of the emerging data on Wnt signaling in bone repair. Disruption of the Wnt pathway greatly inhibits bone formation and the healing process. Interestingly, activation of the Wnt pathway has potential to improve bone healing, but only utilized after mesenchymal cells have become committed to the osteoblast lineage.* —DGL

Goodship AE, Lawes TJ, Rubin CT. Low-magnitude high-frequency mechanical signals accelerate and augment endochondral bone repair: Preliminary evidence of efficacy. *J Orthop Res*. 2008 Dec 30. [Epub ahead of print] [Abstract]

> *This small but very interesting pilot study in sheep examines the effect on fracture healing of 25-μm displacements, induced by a ferroactive shape-memory alloy ("smart" material) incorporated into the body of the external fixator. These movements comprised less than 1% of the 3-mm fracture gap, and less than 6% of the 0.45-mm displacement measured at the site during ambulation. Despite this, at 10-weeks post-op, the callus in the stimulated group was 3.6-fold stiffer, 2.5-fold stronger and 29% larger than controls. BMC was 52% greater in the experimental group. These differences were significant even at n=4. Further work on low magnitude high frequency stimulation is awaited with interest.* —DGL

O'Loughlin PF, Cunningham ME, Bukata SV, Tomin E, Poynton AR, Doty SB, Sama AA, Lane JM. Parathyroid hormone (1-34) augments spinal fusion, fusion mass volume, and fusion mass quality in a rabbit spinal fusion model. *Spine*. 2009 Jan 15;34(2):121-30. [Abstract]

> *This study shows increases in the rate of union and the amount of bone in a standard rabbit model of L5-6 lumbar fusion with a dose of 10 μgrams/kg/day of PTH(1-34). Bone*

and cartilage volume were both significantly increased in the treated group, implying that with further time endochondral ossification could have led to an even larger callus in the PTH group. The only concern one can raise with such work in translation to human medicine is the dose of PTH, which needs to be carefully evaluated in human bone repair trials. —DGL

Tommasini SM, Hu B, Nadeau JH, Jepsen KJ. Phenotypic integration among trabecular and cortical bone traits establishes mechanical functionality of inbred mouse vertebrae. *J Bone Miner Res*. 2008 Dec 8. [Epub ahead of print] [Abstract]

Cortical and trabecular structure and material properties should not be considered in isolation. The authors demonstrate that bone structure and strength are adapted to each other so strains with smaller vertebrae relative to body size increased mineralization and the relative amounts of cortical and trabecular bone within the smaller bone. Variation in trabecular traits is determined in part by the adaptive response to variation in traits describing the cortical shell. —ES

Clinical Studies and Drug Effects

Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J Bone Miner Res*. 2008 Dec 29. [Epub ahead of print] [Abstract]

These authors suggest that subtrochanteric fractures are fragility in type and not related to adverse outcomes of prolonged suppression of remodeling. While the data suggest this, the mean duration of treatment was 2.2 years and over 6 years in only 178 patients. This adverse effect, if it is real, is likely to be very uncommon so most cases of subtrochanteric fractures will not be due to prolonged treatment. Nevertheless, some might be. —ES

Axelrad TW, Steen B, Lowenberg DW, Creevy WR, Einhorn TA. Heterotopic ossification after the use of commercially available recombinant human bone morphogenetic proteins in four patients. *J Bone Joint Surg Br*. 2008 Dec;90(12):1617-22. [Abstract]

A simple report of 4 cases of heterotopic ossification after use of BMP-2 or BMP-7. Symptomatic cases responded well to excision. —DGL

Brennan TC, Rizzoli R, Ammann P. Selective modification of bone quality by PTH, pamidronate or raloxifene. *J Bone Miner Res*. 2008 Dec 8. [Epub ahead of print] [Abstract]

Comparator trials of anabolic and antiresorptives in human subjects are rare. Studies in animals are uncommon. The late Lis Mosekilde and her team published several. This study supports and extends that work. In 8-month old OVX rats, PTH(1-34) induced greater maximal load and absorbed energy than pamidronate (APD) or raloxifene. PTH increased trabecular bone volume and connectivity. APD preserved structure. Raloxifene had no effect on structure but modified material properties. Extrapolating these observations to the human skeleton is not appropriate. —ES

Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, Hadji P, Hofbauer LC, Alvaro-Gracia JM, Wang H, Austin M, Wagman RB, Newmark R, Libanati C, San Martin J, Bone HG. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009 Jan;24(1):153-61. [Abstract]

This new drug suppresses remodeling rapidly and profoundly but totally reversibly. Of great interest is to determine whether there are structural benefits that might be inferred to reduce fractures early and sooner than other drugs. 1,189 postmenopausal women were randomized to denosumab or alendronate. Denosumab increased BMD more at the total hip (3.5% vs. 2.6%) and other sites (12-mo treatment difference: 0.6%, femoral neck; 1.0%, trochanter; 1.1%, lumbar spine; 0.6%, one-third radius; p ≤ 0.0002 all sites) and suppressed remodeling more. —ES

Castillo H, Samson-Fang L; American Academy for Cerebral Palsy and Developmental Medicine Treatment Outcomes Committee Review Panel. Effects of bisphosphonates in children with osteogenesis imperfecta: an AACPDM systematic review. *Dev Med Child Neurol*. 2009 Jan;51(1):17-29. [Abstract]

This study finds that despite a large literature on this topic, very few papers are truly informative. These studies confirm improvement in bone density. Many, but not all studies, demonstrate a reduction in fracture rate and enhanced growth. The optimal medication and dosing regimen, and how long patients should be treated, are unclear. Reports of long-term side effects are only starting to emerge given the time frame of bisphosphonate use in osteogenesis imperfecta. Further trials of efficacy and long-term studies are required. —DGL

Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR. The anti-resorptive effects of a single dose of zoledronate persist for two years: a randomized, placebo-controlled trial in osteopenic postmenopausal women. *J Clin Endocrinol Metab*. 2008 Dec 2. [Epub ahead of print]

A single infusion of zoledronate decreased turnover and increased bone mineral density for at least 2 years. If fracture risk is reduced and sustained then this is an important observation for a range of reasons. It may be important to treat earlier for prevention of nonvertebral fractures. This means exposing individuals at lower short-term but high long-term risk, so treatments must be safe, given at the minimum dosage possible. —ES

Griffin XL, Smith CM, Costa ML. The clinical use of platelet-rich plasma in the promotion of bone healing: A systematic review. *Injury*. 2008 Dec 11. [Epub ahead of print] [Abstract]

Since it is autologous and fairly cheap as compared to recombinant growth factors, platelet-rich plasma (PRP) has been extensively tested in regenerative medicine, including wound and bone repair. Despite extensive clinical use in orthopedics, this systematic review found only five clinically relevant articles. Only one was a randomized controlled trial, but this was underpowered for the outcome measure defined. While early clinical results suggest that PRP is safe and feasible, there is no clinical evidence of benefit in either acute or delayed fracture healing. —DGL

Inderjeeth CA, Foo AC, Lai MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: Review of the evidence. *Bone*. 2008 Dec 16. [Epub ahead of print] [Abstract]

This review shows that the bisphosphonates and teriparatide show vertebral fracture relative risk reductions in the elderly; thus far only trials of strontium ranelate have proven non-vertebral and hip fracture efficacy in older people with osteoporosis. The review raises the issue that more work is necessary to examine if the standard first line treatments are indeed the best for the very elderly with the highest fracture risk. —DGL

Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Lorich DG, Lane JM. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int*. 2008 Dec 9. [Epub ahead of print] [Abstract]

> *Minimal trauma subtrochanteric and femoral shaft fractures in women often under 75 may be causally related to long-term bisphosphonate use. If so, this is very uncommon. Research is needed to identify patients who might be susceptible to this rare adverse event of prolonged remodeling suppression. Characteristics of the patient such as low pre-treatment remodeling may predispose. Also, features including high binding affinity of the drug to mineral and other factors (duration of treatment) may contribute.* —ES

Li X, Ominsky MS, Warmington KS, Morony S, Gong J, Cao J, Gao Y, Shalhoub V, Tipton B, Haldankar R, Chen Q, Winters A, Boone T, Geng Z, Niu QT, Ke HZ, Kostenuik PJ, Simonet WS, Lacey DL, Paszty C. Sclerostin antibody treatment increases bone formation, bone mass and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res*. 2008 Dec 2. [Epub ahead of print] [Abstract]

> *Six-month-old female rats were ovariectomized for one year. A sclerostin neutralizing monoclonal antibody (Scl-AbII) was administered for 5 weeks and increased bone formation on trabecular, periosteal, endocortical and intracortical surfaces reversing structural decay, but also further increased bone mass and bone strength to levels greater than those found in non-ovariectomized control rats. Publication of studies in primates are eagerly awaited.* —ES

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*. 2009 Jan;44(1):113-9. [Abstract]

> *While sample sizes are small, it is interesting to find that PTH(1-84) increases cancellous bone volume (BV/TV) due to higher trabecular number (Tb.N) from intratrabecular tunneling and thickness, but there were no effects on cortical thickness, or endocortical or periosteal BFR, while cortical porosity tended to be higher.* —ES

Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, Constantine GD, Chines AA. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. *J Bone Miner Res*. 2008 Dec;23(12):1923-34. [Abstract]

> *Bazedoxifene 20 or 40 mg/d, raloxifene 60 mg/d, or placebo were studied in 6,847 women. The incidence of new vertebral fractures was 2.3%, 2.5% and 2.3%, respectively, compared with placebo (4.1%), with relative risk reductions of 42%, 37%, and 42%, respectively. Nonvertebral fracture risk was not reduced with bazedoxifene or raloxifene. In a post-hoc analysis (subjects with femoral neck T-score less than or equal to -3.0 and/or greater than or equal to 1 moderate or severe vertebral fracture or multiple mild vertebral fractures; n = 1772), bazedoxifene 20 mg showed a 50% reduction (relative to placebo, p = 0.02) and a 44% reduction (relative to raloxifene, p = 0.05) in nonvertebral fracture risk. The incidence of vasodilatation, leg cramps, and venous thromboembolic events was higher with bazedoxifene and raloxifene than placebo.* —ES

Smektala R, Endres HG, Dasch B, Maier C, Trampisch HJ, Bonnaire F, Pientka L. The effect of time-to-surgery on outcome in elderly patients with proximal femoral fractures. *BMC Musculoskelet Disord*. 2008 Dec 29;9:171. [Abstract]

The interesting thing about this study is that comparison of groups with short (n = 802), medium (n = 1191) and long (n = 923) time-to-surgery showed very few differences in outcome, apart from some post-op complications such as pressure sores. No association between mortality and time-to-surgery was elucidated. This may be because the longest time-to-surgery patients have the highest ASA scores (pre-morbidity) and the time to stabilize them may have been advantageous. —DGL

Warden SJ, Komatsu DE, Rydberg J, Bond JL, Hassett SM. Recombinant human parathyroid hormone (PTH 1-34) and low-intensity pulsed ultrasound have contrasting additive effects during fracture healing. *Bone*. 2008 Nov 21. [Epub ahead of print] [Abstract]

This study investigated the individual and combined effects of PTH and low-intensity pulsed ultrasound (LIPUS) on fracture healing. In a rat model using bilateral midshaft femur fractures, animals were treated 7 days/week with PTH (10 μg/kg) or vehicle. Each animal also had one fracture treated for 20 min/day with active-LIPUS and the contralateral fracture treated with inactive-LIPUS placebo. Large differences were seen with PTH treatment as in other studies. The callus was more dense, but not larger. The callus was larger, but more immature, in the LIPUS group, with retention of cartilage matrix. Thus PTH-treated calluses were stronger, but LIPUS-treated calluses were not. The addition of LIPUS to PTH treatment, if anything, delayed healing maturation and did not add to mechanical properties. —DGL

Weinstein RS, Roberson PK, Manolagas SC. Giant osteoclast formation and long-term oral bisphosphonate therapy. *N Engl J Med*. 2009 Jan 1;360(1):53-62. [Abstract]

Long-observed, never formally reported, the frustrated osteoclasts that appear with bisphosphonate treatment finally make it to the New England Journal of Medicine. Here 50 bone biopsies taken from young postmenopausal women receiving various doses of daily alendronate for up to 3 years were analyzed. Alendronate increased osteoclast numbers on and adjacent to the bone surface and caused the appearance of giant, hypernucleated osteoclasts detached from the bone surface, 20 to 37% of which were apoptotic. These changes did not persist one year after drug removal. The biological mechanisms and relevance of these findings, if any, are unknown. —SF

Genetics

Eriksson AL, Lorentzon M, Vandenput L, Labrie F, Lindersson M, Syvänen AC, Orwoll ES, Cummings SR, Zmuda JM, Ljunggren O, Karlsson MK, Mellström D, Ohlsson C. Genetic variations in sex steroid-related genes as predictors of serum estrogen levels in men. *J Clin Endocrinol Metab*. 2008 Dec 30. [Epub ahead of print]

This large candidate gene study from the GOOD and MrOS cohorts confirms that a polymorphism in the CYP19 (aromatase) gene is associated with LS BMD and self-reported fractures, and demonstrates that this polymorphism is associated with estradiol levels in men. —SF

Tang PL, Cheung CL, Sham PC, McClurg P, Lee B, Chan SY, Smith DK, Tanner JA, Su AI, Cheah KS, Kung AW, Song YQ. Genome-wide haplotype association mapping in mice identifies a genetic variant in CER1 associated with bone mineral density and fracture in southern Chinese women. *J Bone Miner Res*. 2008 Dec 29. [Epub ahead of print] [Abstract]

This study reported a haplotype block within Cer1A important to bone mineral density (BMD) in mice. Furthermore, a non-synonymous SNP in human CER1 was associated

with increased risk of both low BMD in premenopausal women (OR 2.2; 95% confidence interval: 1.0 - 4.6; p < 0.05) and increased risk of vertebral fractures (OR 1.82, p=0.025) in postmenopausal women. Along with functional evidence, this study may suggest a role of CER1 in the development of bone or its metabolism. —HWD

Molecular and Cell Biology

Choi SJ, Roodman GD, Feng JQ, Song IS, Amin K, Hart PS, Wright JT, Haruyama N, Hart TC. In vivo impact of a 4 bp deletion mutation in the DLX3 gene on bone development. *Dev Biol*. 2009 Jan 1;325(1):129-37. [Abstract]

Transgenic mice expressing in osteoblasts a deletion mutant of DLX3, previously implicated in the osteosclerotic/osteopetrotic features of the tricho-dento-osseous syndrome (TDO), showed deficient osteoclastogenesis and increased IFN-γ levels and expression. This observation establishes the molecular basis for TDO and further demonstrates that IFN-γ represses, rather than stimulates, osteoclastogenesis. —SF

Hesslein DG, Fretz JA, Xi Y, Nelson T, Zhou S, Lorenzo JA, Schatz DG, Horowitz MC. Ebf1-dependent control of the osteoblast and adipocyte lineages. *Bone*. 2008 Dec 16. [Epub ahead of print] [Abstract]

Early B cell factor 1 (Ebf1) is known as a transcription factor necessary for the development of this cell lineage, and the adipocytic lineage as well. This study reports that Ebf1 is also expressed in osteoblasts. In contrast to PPARγ(+/-) mice who make osteoblasts rather than adipocytes, Ebf1 KO mice are now shown to have increased osteoblast numbers and bone formation, but also increased bone marrow adipogenesis. Hence, adipogenesis in the bone environment does not necessarily occur at the expense of osteoblastogenesis. —SF

Yu PB, Deng DY, Lai CS, Hong CC, Cuny GD, Bouxsein ML, Hong DW, McManus PM, Katagiri T, Sachidanandan C, Kamiya N, Fukuda T, Mishina Y, Peterson RT, Bloch KD. BMP type I receptor inhibition reduces heterotopic ossification. *Nat Med*. 2008 Dec;14(12):1363-9. [Abstract]

Patients with fibrodysplasia ossificans progressiva (FOP) harbor activating mutations in the BMPR1 (ALK2) gene. Muscular postnatal overexpression of a transgene encoding constitutively active ALK2 (caALK2) is induced by intramuscular injections of adenovirus specifying Cre (Ad.Cre), leading to local inflammation and ectopic endochondral bone formation in mice recapitulating FOP. A selective BMPR1 inhibitor, LDN-193189, inhibits activation of Smad1/5/8 and reduces ectopic ossification in tissues expressing caALK2. Expression of caALK2 without inflammation does not lead to ectopic ossification. These results demonstrate that both caALK2 expression and inflammation are required for the development of ectopic ossification, and suggest that a BMPR1 inhibitor may be useful in the treatment of FOP. —TM

Yu S, Bruce D, Froicu M, Weaver V, Cantorna MT. Failure of T cell homing, reduced CD4/CD8alphaalpha intraepithelial lymphocytes, and inflammation in the gut of vitamin D receptor KO mice. *Proc Natl Acad Sci U S A*. 2008 Dec 30;105(52):20834-9. [Abstract] [Full Text]

Inflammatory bowel disease (IBD) induction in IL-10/vitamin D receptor (VDR) double knockout (DKO) mice is severe even under specific pathogen free (SPF) conditions. CD4 regulatory T cell development and function are normal in VDR KO mice. The impaired suppression of IBD by VDR KO CD4 T cells is not due to increased induction of pathogenic Th17 or Th1 cells in the gut, but is associated with the decreased expression

of CCR9 and reduced homing of VDR KO T cells to intraepithelial lymphocytes (IEL). The IEL of the VDR KO mice are missing CD4/CD8αα T cells, have half as many CD8αα IEL cells and as a result low IL-10 production in the IBL. Thus, the VDR mediates T cell homing to the gut and VDR KO mice have reduced CD8αα IEL numbers with low IL-10 levels leading to increased inflammatory responses even under SPF conditions. —TM

Physiology and Metabolism

Hinoi E, Gao N, Jung DY, Yadav V, Yoshizawa T, Myers MG Jr, Chua SC Jr, Kim JK, Kaestner KH, Karsenty G. The sympathetic tone mediates leptin's inhibition of insulin secretion by modulating osteocalcin bioactivity. *J Cell Biol*. 2008 Dec 29;183(7):1235-42. [Abstract] [Full Text]

Following on their seminal discovery that osteocalcin regulates insulin secretion and energy metabolism, i.e., a bone-to-fat endocrine axis, these authors now report that β-adrenergic receptor-mediated effects of central leptin inhibit osteocalcin production by osteoblasts, hence providing a negative feedback loop on insulin secretion and glucose sensitivity. —SF

Kindblom JM, Ohlsson C, Ljunggren O, Karlsson MK, Tivesten A, Smith U, Mellström D. Plasma osteocalcin is inversely related to fat mass and plasma glucose in elderly Swedish men. *J Bone Miner Res*. 2008 Dec 8. [Epub ahead of print] [Abstract]

In 1,010 men (non-diabetic, n=857 and diabetic, n=153), diabetics had 21.7% lower plasma osteocalcin than non-diabetics. For all subjects and non-diabetics, plasma osteocalcin was inversely related to BMI, fat mass and plasma glucose. Plasma osteocalcin explained 6.3% of the variance in plasma glucose while it associated moderately with serum insulin. Multiple linear regression models adjusting for serum insulin and fat mass demonstrated that plasma osteocalcin was an independent negative predictor of plasma glucose (p<0.001). —ES

Miao D, Su H, He B, Gao J, Xia Q, Zhu M, Gu Z, Goltzman D, Karaplis AC. Severe growth retardation and early lethality in mice lacking the nuclear localization sequence and C-terminus of PTH-related protein. *Proc Natl Acad Sci U S A*. 2008 Dec 23;105(51):20309-14. [Abstract] [Full Text]

Knock-in mice expressing a truncated form of PTHrP(1-84), i.e., lacking the C-terminal and nuclear localization sequence, present a very distinct phenotype from that of PTHrP null mice, i.e., they are normal at birth, without limb shortening or tooth eruption defects, but then rapidly develop a failure to thrive and signs of premature aging in multiple organs (progeroid phenotype). Osteoblast and osteoclast numbers were decreased. These results ascribe a new and important physiological role to the distal portion of PTHrP, emphasizing the notion that the PTHrP gene codes for multiple transcripts and proteins with pleiotropic functions. —SF

Shi Y, Yadav VK, Suda N, Liu XS, Guo XE, Myers MG Jr, Karsenty G. Dissociation of the neuronal regulation of bone mass and energy metabolism by leptin in vivo. *Proc Natl Acad Sci U S A*. 2008 Dec 23;105(51):20529-33. [Abstract] [Full Text]

Deletion of the leptin receptor in neurons (not osteoblasts) increases remodeling, resulting in high bone mass as seen in leptin-deficient mice. l/l mice with a Y985L substitution in the leptin receptor produce a gain-of-function in leptin signaling inhibiting bone mass accrual by up-regulating sympathetic activity independent of appetite or

energy expenditure. Leptin regulates bone mass accrual through neuronal means independent of its regulation of energy metabolism. —ES

Public Health

Donaldson M, Cawthon P, Lui L, Schousboe J, Ensrud K, Taylor B, Cauley J, Hillier T, Black D, Bauer D, Cummings S; for the Study of Osteoporotic Fractures. Estimates of the proportion of older white women who would be recommended for pharmacologic treatment by the new US National Osteoporosis Foundation guidelines. *J Bone Miner Res*. 2008 Dec 2. [Epub ahead of print] [Abstract]

The new US National Osteoporosis Foundation Clinician's Guide criteria for treatment based on history of fracture, BMD T-scores ≤-2.5, presence of low bone mass plus a 10 year risk of hip fracture ≥3% or major osteoporotic fracture ≥20%, if applied to the SOF data, estimate that approximately 72% of US white women ≥ age 65 and 93% of those ≥ age 75 years would be recommended for treatment. The question is, what would be the net cost and quality of fracture-free life years gained? —ES

Reviews, Perspectives and Editorials

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*. 2009 Jan;124(6):561-77. [Abstract]

Other Studies of Potential Interest

Alonso V, de Gortázar AR, Ardura JA, Andrade-Zapata I, Alvarez-Arroyo MV, Esbrit P. Parathyroid hormone-related protein (107-139) increases human osteoblastic cell survival by activation of vascular endothelial growth factor receptor-2. *J Cell Physiol*. 2008 Dec;217(3):717-27. [Abstract]

Atsawasuwan P, Mochida Y, Katafuchi M, Kaku M, Fong KS, Csiszar K, Yamauchi M. Lysyl oxidase binds transforming growth factor-beta and regulates its signaling via amine oxidase activity. *J Biol Chem*. 2008 Dec 5;283(49):34229-40. [Abstract] [Full Text]

Baron RA, Tavare R, Figueiredo AC, Blazewska K, Kashemirov BA, McKenna CE, Ebetino FH, Taylor A, Rogers MJ, Coxon FP, Seabra MC. Phosphonocarboxylates inhibit the second geranylgeranyl addition by Rab geranylgeranyl transferase. *J Biol Chem*. 2008 Dec 11. [Epub ahead of print]

Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman JM, Reginster JY, Gangji V; Members of Advisory Board on Bone Markers. Evidence-based guidelines for the use of biochemical markers of bone turnover in the selection and monitoring of bisphosphonate treatment in osteoporosis: a consensus document of the Belgian Bone Club. *Int J Clin Pract*. 2009 Jan;63(1):19-26.

Bradley EW, Ruan MM, Oursler MJ. PAK1 is a novel MEK-independent raf target controlling expression of the IAP survivin in M-CSF-mediated osteoclast survival. *J Cell Physiol*. 2008 Dec;217(3):752-8. [Abstract]

Chevalley T, Bonjour JP, Ferrari S, Rizzoli R. Deleterious effect of late menarche on distal tibia microstructure in healthy 20-year-old and premenopausal middle-aged women. *J Bone Miner Res*. 2009 Jan;24(1):144-52. [Abstract]

Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. *J Bone Miner Res*. 2008 Dec 29. [Epub ahead of print] [Abstract]

Dhawan P, Wieder R, Christakos S. CCAAT enhancer-binding protein alpha is a molecular target of 1,25-dihydroxyvitamin D3 in MCF-7 breast cancer cells. *J Biol Chem*. 2009 Jan 30;284(5):3086-95. [Abstract] [Full Text]

Gutierrez GM, Kong E, Sabbagh Y, Brown NE, Lee JS, Demay MB, Thomas DM, Hinds PW. Impaired bone development and increased mesenchymal progenitor cells in calvaria of RB1-/- mice. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18402-7. [Abstract] [Full Text]

Haÿ E, Laplantine E, Geoffroy V, Frain M, Kohler T, Müller R, Marie PJ. N-cadherin interacts with axin and LRP5 to negatively regulate Wnt/beta-catenin signaling, osteoblast function, and bone formation. *Mol Cell Biol*. 2009 Feb;29(4):953-64. [Abstract]

Hohenester E, Sasaki T, Giudici C, Farndale RW, Bächinger HP. Structural basis of sequence-specific collagen recognition by SPARC. *Proc Natl Acad Sci U S A*. 2008 Nov 25;105(47):18273-7. [Abstract] [Full Text]

Hurtel-Lemaire 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 signaling pathways. *J Biol Chem*. 2009 Jan 2;284(1):575-84. [Abstract] [Full Text]

Jenkins ZA, van Kogelenberg M, Morgan T, Jeffs A, Fukuzawa R, Pearl E, Thaller C, Hing AV, Porteous ME, Garcia-Miñaur S, Bohring A, Lacombe D, Stewart F, Fiskerstrand T, Bindoff L, Berland S, Adès LC, Tchan M, David A, Wilson LC, Hennekam RC, Donnai D, Mansour S, Cormier-Daire V, Robertson SP. Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. *Nat Genet*. 2009 Jan;41(1):95-100. [Abstract]

Kanazawa I, Yamaguchi T, Yamamoto M, Yamauchi M, Kurioka S, Yano S, Sugimoto T. Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2009 Jan;94(1):45-9. [Abstract] [Full Text]

Kumarasuriyar A, Grøndahl L, Nurcombe V, Cool SM. Osteoblasts up-regulate the expression of extracellular proteases following attachment to Poly(beta-hydroxybutyrate-co-beta-hydroxyvalerate). *Gene*. 2009 Jan 1;428(1-2):53-8. [Abstract]

Kuss P, Villavicencio-Lorini P, Witte F, Klose J, Albrecht AN, Seemann P, Hecht J, Mundlos S. Mutant Hoxd13 induces extra digits in a mouse model of synpolydactyly directly and by decreasing retinoic acid synthesis. *J Clin Invest*. 2009 Jan;119(1):146-56. [Abstract]

Lo Celso C, Fleming HE, Wu JW, Zhao CX, Miake-Lye S, Fujisaki J, Côté D, Rowe DW, Lin CP, Scadden DT. Live-animal tracking of individual haematopoietic stem/progenitor cells in their niche. *Nature*. 2009 Jan 1;457(7225):92-6. [Abstract]

Miraoui H, Oudina K, Petite H, Tanimoto Y, Moriyama K, Marie PJ. Fibroblast growth factor receptor2 promotes osteogenic differentiation in mesenchymal cells via extracellular-related kinase and protein kinase c signalling. *J Biol Chem*. 2008 Dec 30. [Epub ahead of print]

Miyazaki T, Miyauchi S, Tawada A, Anada T, Matsuzaka S, Suzuki O. Oversulfated chondroitin sulfate-E binds to BMP-4 and enhances osteoblast differentiation. *J Cell Physiol*. 2008 Dec;217(3):769-77. [Abstract]

Pederson L, Ruan M, Westendorf JJ, Khosla S, Oursler MJ. Regulation of bone formation by osteoclasts involves Wnt/BMP signaling and the chemokine sphingosine-1-phosphate. *Proc Natl Acad Sci U S A*. 2008 Dec 30;105(52):20764-9. [Abstract] [Full Text]

Popp AW, Senn C, Franta O, Krieg MA, Perrelet R, Lippuner K. Tibial or hip BMD predict clinical fracture risk equally well: results from a prospective study in 700 elderly Swiss women. *Osteoporos Int*. 2008 Dec 19. [Epub ahead of print]

Sabbieti MG, Agas D, Xiao L, Marchetti L, Coffin JD, Doetschman T, Hurley MM. Endogenous FGF-2 is critically important in PTH anabolic effects on bone. *J Cell Physiol*. 2009 Apr;219(1):143-51. [Abstract]

Serrat MA, King D, Lovejoy CO. Temperature regulates limb length in homeotherms by directly modulating cartilage growth. *Proc Natl Acad Sci U S A*. 2008 Dec 9;105(49):19348-53. [Abstract] [Full Text]

Sharff KA, Song WX, Luo X, Tang N, Luo J, Chen J, Bi Y, He BC, Huang J, Li X, Jiang W, Zhu GH, Su Y, He Y, Shen J, Wang Y, Chen L, Zuo GW, Liu B, Pan X, Reid RR, Luu HH, Haydon RC, He TC. Hey1 basic helix-loop-helix protein plays an important role in mediating BMP9-induced osteogenic differentiation of mesenchymal progenitor cells. *J Biol Chem*. 2009 Jan 2;284(1):649-59. [Abstract] [Full Text]

Sugatani T, Hruska K. Impaired microRNA pathways diminish osteoclast differentiation and function. *J Biol Chem*. 2008 Dec 5. [Epub ahead of print]

Sun F, Xie Q, Ma J, Yang S, Chen Q, Hong A. Nuclear factor Y is required for basal activation and chromatin accessibility of fibroblast growth factor receptor 2 promoter in osteoblast-like cells. *J Biol Chem*. 2009 Jan 30;284(5):3136-47. [Abstract] [Full Text]

Topol L, Chen W, Song H, Day TF, Yang Y. Sox9 inhibits Wnt signaling by promoting beta--catenin phosphorylation in the nucleus. *J Biol Chem*. 2009 Jan 30;284(5):3323-33. [Abstract] [Full Text]

Verhaar HJ, Lems WF. PTH-analogs: Comparable or different? *Arch Gerontol Geriatr*. 2009 Jan 3. [Epub ahead of print] [Abstract]

Viegas CS, Simes DC, Laizé 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 Dec 26;283(52):36655-64. [Abstract] [Full Text]

Wei J, Sheng X, Feng D, McGrath B, Cavener DR. PERK is essential for neonatal skeletal development to regulate osteoblast proliferation and differentiation. *J Cell Physiol*. 2008 Dec;217(3):693-707. [Abstract]

Wu S, Fadoju D, Rezvani G, De Luca F. Stimulatory effects of insulin-like growth factor-I on growth plate chondrogenesis are mediated by nuclear factor-kappaB p65. *J Biol Chem*. 2008 Dec 5;283(49):34037-44. [Abstract] [Full Text]

Wu X, Lemon B, Li X, Gupte J, Weiszmann J, Stevens J, Hawkins N, Shen W, Lindberg R, Chen JL, Tian H, Li Y. C-terminal tail of FGF19 determines its specificity toward Klotho co-receptors. *J Biol Chem*. 2008 Nov 28;283(48):33304-9. [Abstract] [Full Text]

Xie Y, Yin T, Wiegraebe W, He XC, Miller D, Stark D, Perko K, Alexander R, Schwartz J, Grindley JC, Park J, Haug JS, Wunderlich JP, Li H, Zhang S, Johnson T, Feldman RA, Li L.

Detection of functional haematopoietic stem cell niche using real-time imaging. *Nature*. 2009 Jan 1;457(7225):97-101. [Abstract]

Xu Z, Hurchla MA, Deng H, Uluckan O, Bu F, Berdy A, Eagleton MC, Heller EA, Floyd DH, Dirksen WP, Shu S, Tanaka Y, Fernandez SA, Rosol TJ, Weilbaecher KN. Interferon-gamma targets cancer cells and osteoclasts to prevent tumor associated bone loss and bone metastases. *J Biol Chem*. 2008 Dec 5. [Epub ahead of print]

Yun SI, Yoon HY, Jeong SY, Chung YS. Glucocorticoid induces apoptosis of osteoblast cells through the activation of glycogen synthase kinase 3beta. *J Bone Miner Metab*. 2008 Dec 5. [Epub ahead of print] [Abstract]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and is an advisory committee member and lectures occasionally at conference symposia for Merck Sharp & Dohme, the Alliance for Better Bone Health (Sanofi Aventis/P&G), Amgen, Eli Lilly (Switzerland), Servier (Switzerland), and Novartis (Switzerland). 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.