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NOT TO BE MISSED

Clinical and Basic Research Papers – June 2008

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Bone Modeling, Remodeling and Repair

Jacobsen KA, Al-Aql ZS, Wan C, Fitch JL, Stapleton SN, Mason ZD, Cole RM, Gilbert SR, Clemens TL, Morgan EF, Einhorn TA, Gerstenfeld LC. Bone formation during distraction osteogenesis is dependent on both VEGFR1 and VEGFR2 signaling. *J Bone Miner Res*. 2008 May;23(5):596-609. [Abstract]

> *Treatment with antibodies to VEGFR1 (Flt-1) and VEGFR2 (Flk-1) or only VEGFR2 was examined in murine distraction osteogenesis. MicroCT evaluation of bone formation revealed a significant decrease with the double antibody treatment and a smaller decrease with single antibody treatment. Vessel volume, number, and connectivity showed progressive and significant inhibition between the single and double antibody blockade. A very interesting finding, corroborated by other work, was that single antibody blockade led to chondrogenesis dominating over osteogenesis. This suggests that oxygen tension is important to cell fate decision in bone repair in vivo. Double blockade produced a failure of both processes.* —DGL

Kogianni G, Mann V, Noble BS. Apoptotic bodies convey activity capable of initiating osteoclastogenesis and localized bone destruction. *J Bone Miner Res*. 2008 Jun;23(6):915-27. [Abstract]

> *The first event in bone remodeling is not known. The growing awareness of the osteocyte as the likely conductor of the orchestral concert of bone remodeling is an exciting advance in our understanding and Dr. Noble has made important contributions in this area. In this study, the investigators report that osteocyte apoptosis precedes osteoclastic bone resorption and that apoptotic osteocytes support osteoclastogenesis and osteoclastic bone resorption in vivo and in vitro, indicating that the site-specific apoptotic death of osteocytes underlies the mechanism by which targeted remodeling is initiated in bone.* —ES

Kubota T, Michigami T, Sakaguchi N, Kokubu C, Suzuki A, Namba N, Sakai N, Nakajima S, Imai K, Ozono K. An Lrp6 hypomorphic mutation affects bone mass through bone resorption in mice and impairs interaction with Mesd. *J Bone Miner Res*. 2008 May 27; [Epub ahead of print] [Abstract]

> *It has been well-documented that low-density lipoprotein receptor-related protein 5 (LRP5) regulates bone acquisition by controlling bone formation; however, roles of another co-receptor for Wnts, LRP6, in postnatal bone metabolism have not been fully elucidated. Kubota et al. investigated the bone phenotype in mice harboring an Lrp6 hypomorphic mutation, ringelschwanz (rs), and characterized the mutant protein. Their results indicate that Lrp6-mediated signaling controls postnatal bone mass, at least*

partly through the regulation of bone resorption. It is interesting that LRP5 and LRP6 regulate bone metabolism in different ways. —HWD

Cancer and Bone

Lin SH, Cheng CJ, Lee YC, Ye X, Tsai WW, Kim J, Pasqualini R, Arap W, Navone NM, Tu SM, Hu M, Yu-Lee LY, Logothetis CJ. A 45-kDa ErbB3 secreted by prostate cancer cells promotes bone formation. *Oncogene*. 2008 May 19; [Epub ahead of print] [Abstract]

ErbB3 is a growth factor receptor that promotes cancer growth. An alternatively spliced truncated variant of ErbB3 encoding a 45 kDa soluble protein (p45-sErbB3) is upregulated in metastatic cells in bone and lymph nodes but not in the primary prostate cancer. This paper demonstrates that recombinant p45-sErbB3 stimulates osteoblast differentiation and bone formation. Overexpression of p45-sErbB3 in an osteolytic prostate cancer cell line, PC-3, converts its phenotype to an osteoblastic one in a mouse xenograft model. In addition, p45-sErbB3 is detected in plasma from castration-resistant prostate cancer patients with bone metastases. These data suggest that p45-sErbB3 is among the factors involved in the osteoblastic bone metastases of prostate cancer. Elucidation of the regulation of production, as well as the mechanism of action, of p45-sErbB3 may open up a new approach for the treatment of the osteoblastic metastases of prostate cancer. —TM

Qiang YW, Chen Y, Stephens O, Brown N, Chen B, Epstein J, Barlogie B, Shaughnessy JD Jr. Myeloma-derived Dickkopf-1 disrupts Wnt-regulated osteoprotegerin and RANKL production by osteoblasts: a potential mechanism underlying osteolytic bone lesions in multiple myeloma. *Blood*. 2008 Feb 27; [Epub ahead of print]

In the bone marrow of multiple myeloma (MM) patients, the RANKL/OPG ratio is elevated, and restoring the normal RANKL/OPG ratio not only reduces lytic MM bone lesions but also suppresses disease progression. The authors previously reported that MM cells express DKK-1, an antagonist of the canonical Wnt pathway. Because DKK-1 inhibits Wnt-regulated osteoblast (OB) maturation, and because RANKL is expressed in premature OBs and OPG is expressed by mature OBs, MM cell-derived DKK-1 may suppress OB maturation and thereby increase the RANKL/OPG ratio. In this report, the authors demonstrate that DKK-1 abolishes Wnt3a-induced OPG production in OBs, and that bone marrow sera from MM patients suppress Wnt3a-induced OPG expression and enhance RANKL expression in a DKK1-dependent manner. These observations suggest a key role for DKK-1 in the development of the lytic bone lesions of MM by interrupting canonical Wnt signal-induced OB maturation. —TM

Clinical Studies and Drug Effects

Allen MR, Reinwald S, Burr DB. Alendronate reduces bone toughness of ribs without significantly increasing microdamage accumulation in dogs following 3 years of daily treatment. *Calcif Tissue Int*. 2008 May 8; [Epub ahead of print] [Abstract]

This paper builds on the work, by the same group, on long-term alendronate use in beagle dogs by examining the ribs as long bones (the previous study was related to vertebral fracture). Skeletally mature intact beagle dogs were treated daily for 3 years with vehicle (VEH), alendronate 0.2 mg/kg (ALN0.2), or alendronate 1.0 mg/kg (ALN1.0). The lower dose approximates osteoporosis dosing and the higher dose an increased dose. Toughness was significantly lower with ALN1.0 high-dose treatment (-33%) but not with ALN0.2 (-19%), compared to VEH, while neither ultimate stress nor modulus differed

between the groups. While the toughness was different, there was no significant difference in overall microdamage accumulation between any of the groups. The study examines important methodologic differences between other studies in the literature, including both pre- and post-yield toughness in the analysis. While animal studies cannot prove a link between bisphosphonates and bone toughness, they may highlight the mechanisms if human data are confirmed. The main point is that toughness can be different without any difference in microdamage, which highlights the fact that other mechanisms, such as mineralization or collagen cross-linking, may explain any altered material properties after long-term use. —DGL

Caverzasio J, Higgins L, Ammann P. Prevention of trabecular bone loss induced by estrogen deficiency by a selective p38alpha inhibitor. *J Bone Miner Res*. 2008 Apr 28; [Epub ahead of print] [Abstract]

Estrogen deficiency is mediated by cytokines such as TNF-α and IL-1. The p38 pathway mediates the effects of cytokines so the selective p38α inhibitor, SD-282, was assessed during 8 weeks and found to blunt the increase in DPD/Cr induced by OVX in adult rats. SD-282 enhanced by two-fold the rise in serum osteocalcin, blocked vertebral bone loss, reduced trabecular bone loss in long bones, and enhanced cross-sectional area rise of the diaphysis. Whether this opens doors to differing action of drugs on bone formation and resorption is difficult to say; markers of "formation" and "resorption" are not the same as histological evidence of resorption at the tissue and cellular (BMU) levels. —ES

Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, van der Heijde D, Zhou L, Tsuji W, Newmark R; Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum*. 2008 May;58(5):1299-309. [Abstract]

This study demonstrates that in patients with established, erosive RA, and treated with conventional MTX therapy, denosumab 60 or 180 mg every 6 months significantly decreases erosive surfaces (by MRI and Sharp score) without affecting clinical progression of the disease. Although the latter, negative result could be due to the rather limited duration of the observation (12 months), these results support pre-clinical evidence that RANKL inhibition will halt osteoclast-mediated destruction of peri-articular surfaces without affecting the inflammatory process itself. Thereby, it shows the potential benefits and limitations of denosumab in RA treatment. —SF

Fuchs RK, Phipps RJ, Burr DB. Recovery of trabecular and cortical bone turnover following discontinuation of risedronate and alendronate therapy in ovariectomized rats. *J Bone Miner Res*. 2008 May 8; [Epub ahead of print] [Abstract]

Are all bisphosphonates the same? Of course not. Alendronate (ALN) and risedronate (RIS) were given to 6-month-old OVX rats. Turnover rates were suppressed similarly – not more with alendronate – but 16 weeks after withdrawal, trabecular BFR/BS in the proximal tibia was re-established in post-RIS animals but not in post-ALN animals, relative to controls (but not relative to each other). BMD of the 5th lumbar vertebra remained higher than controls in post-ALN animals but not in post-RIS animals. The notion that ALN suppresses remodeling more than RIS is not well-founded, however, the evidence of persistent suppression following cessation of treatment has a better evidence base. —ES

Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med*. 2008 Apr 28;168(8):826-31. [Abstract]

> *Arrhythmias and osteoporosis occur in elderly persons so the possibility exists that the association between atrial fibrillation (AF) and bisphosphonate use, particularly when using zoledronic acid, is the result of a coincidence of aging of bone and heart. This population-based, case-control study identified 719 women with AF and 966 controls without AF, selected at random and matched on age and blood pressure. More cases with AF than controls had ever used alendronate (6.5% [n = 47] vs 4.1% [n = 40]; P = .03) producing an odds ratio of 1.86 (95% CI, 1.09-3.15) after adjustment. This sort of "evidence" is weak and the inference the authors make that 3% of incident AF in this population might be explained by alendronate use might be looked at through a glass darkly. Compare this study with the data reported by Sørenson et al. (BMJ. 2008 Apr 12;336(7648):813-6) who report no greater exposure to etidronate or alendronate among 13,586 cases with AF than 68,054 controls. Where does truth lie?* —ES

McCloskey EV, Vasireddy S, Threlkeld J, Eastaugh J, Parry A, Bonnet N, Beneton M, Kanis JA, Charlesworth D. Vertebral fracture assessment (VFA) with a densitometer predicts future fractures in elderly women unselected for osteoporosis. *J Bone Miner Res*. 2008 May 27; [Epub ahead of print] [Abstract]

> *This study is the first to evaluate the prevalence of morphometric vertebral fractures by DXA-VFA in a large sample (n > 5000) of older (75+) women and to demonstrate that vertebral fractures detected by VFA predict incidental fracture risk both at the spine and hip. The somewhat lower than expected prevalence of vertebral fractures by VFA assessment in this study (15%), compared to the expected prevalence in older women, may be explained by a recruitment bias (a healthier cohort than the general population) and/or by a lower sensitivity of VFA, compared to conventional radiology.* —SF

Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. *J Orthop Trauma*. 2008 May-Jun;22(5):346-50. [Abstract]

> *This study reports an assumed increase in a particular type of subtrochanteric and femoral shaft fracture in women taking alendronate. The study retrospectively reviews AO Type 32, as well as Type 31 A3 fractures, and whether these occurred with low-energy trauma (fall from standing height or less). AO Type 31 A2 fractures (pertrochanteric) were excluded. The data strongly suggest a link between transverse brittle or stress type fractures and alendronate use. However, while the inclusion criteria may be useful to highlight that the vast majority of patients who displayed transverse fractures through thick cortices 32 A3.1 and A3.2 were on alendronate, and that the vast majority of A 31 A3.3 (trochanteric with subtrochanteric extension) were not on alendronate, the failure to include intertrochanteric fractures leaves out an important denominator. If one accepts the as yet unproven link between these transverse fractures and alendronate, we still need to know the baseline hip fracture presentations to get an idea of how common the problem is. If a link is established, the number needed to treat (NNT) for alendronate for hip fractures needs to be compared to the number needed to harm (NNH) for these fractures to determine the overall benefit of alendronate therapy in femoral fractures. Further association studies are required.* —DGL

Genetics

Alimohammadi M, Björklund P, Hallgren A, Pöntynen N, Szinnai G, Shikama N, Keller MP, Ekwall O, Kinkel SA, Husebye ES, Gustafsson J, Rorsman F, Peltonen L, Betterle C,

Perheentupa J, Akerström G, Westin G, Scott HS, Holländer GA, Kämpe O. Autoimmune polyendocrine syndrome type 1 and NALP5, a parathyroid autoantigen. *N Engl J Med*. 2008 Mar 6;358(10):1018-28. [Abstract]

> *Autoimmune polyendocrine syndrome type 1 (APS-1, see OMIM 240300) is a rare polyendocrine disorder due to AIRE mutations. By screening a parathyroid gland cDNA library with serum from APS-1 patients, the authors identified a parathyroid cell cytoplasmic antigen, NALP5, that is the target for autoantibodies present in 50% of APS-1 patients with hypoparathyroidism. Although multiple control groups, including isolated hypoparathyroidism, demonstrate that these antibodies are very specific for APS-1, they suggest that NALP5 mutations could be involved in other hypoparathyroid disorders. To be followed....* —SF

Ferlin A, Pepe A, Gianesello L, Garolla A, Feng S, Giannini S, Zaccolo M, Facciolli A, Morello R, Agoulnik AI, Foresta C. Mutations in the insulin-like factor 3 receptor are associated with osteoporosis. *J Bone Miner Res*. 2008 May;23(5):683-93. [Abstract]

> *Insulin-like factor 3 (INSL3) is produced primarily by testicular Leydig cells. It acts by binding to its specific G protein-coupled receptor RXFP2 (relaxin family peptide 2) and is involved in testicular descent during fetal development. Thus far, the physiological role of INSL3 in adults is not known, although substantial INSL3 circulating levels are present. This study fills this gap by suggesting for the first time a role for INSL3/RXFP2 signaling in bone metabolism and links RXFP2 gene mutations with human osteoporosis, thus providing a new clue for pathological mechanisms of osteoporois.* —HWD

Molecular and Cell Biology

Balemans W, Piters E, Cleiren E, Ai M, Van Wesenbeeck L, Warman ML, Van Hul W. The binding between sclerostin and LRP5 is altered by DKK1 and by high-bone mass LRP5 mutations. *Calcif Tissue Int*. 2008 Jun 3; [Epub ahead of print] [Abstract]

> *This paper clarifies the respective roles of SOST and DKK-1 on the inhibition of Wnt-LRP5 signaling. In particular, it demonstrates, through a series of in vitro experiments, that both antagonists are prevented from exerting their functions when LRP5 carries HBM mutations. Furthermore, co-immunoprecipitation experiments indicate that sclerostin and DKK-1 act as competitive inhibitors of LRP5.* —SF

Ellwanger K, Saito H, Clément-Lacroix P, Maltry N, Niedermeyer J, Lee WK, Baron R, Rawadi G, Westphal H, Niehrs C. Targeted disruption of the Wnt regulator Kremen induces limb defects and high bone density. *Mol Cell Biol*. 2008 May 27; [Epub ahead of print]

> *One further step towards the understanding of the molecules that regulate Wnt signaling, this study demonstrates that mice lacking Kremen 1 and 2, the transmembrane molecules that are responsible for LRP5 endocytosis/inactivation upon DKK-1 binding, have increased osteoblast surfaces, bone formation indices and trabecular bone volume.* —SF

Hounoki H, Sugiyama E, Mohamed SG, Shinoda K, Taki H, Abdel-Aziz HO, Maruyama M, Kobayashi M, Miyahara T. Activation of peroxisome proliferator-activated receptor gamma inhibits TNF-alpha-mediated osteoclast differentiation in human peripheral monocytes in part via suppression of monocyte chemoattractant protein-1 expression. *Bone*. 2008 Apr;42(4):765-74. [Abstract]

Although PPAR-γ activation by glitazones has been shown to be deleterious to bone mass, structure and strength in both rodents and humans, these new data indicate that these agents may reduce osteoclast development from circulating monocytes, as usually induced by TNF-α. Hence glitazones could exert opposing effects on the mechanisms of bone remodeling systemically and within bone (marrow, where they promote adipogenesis over osteoblastogenesis). —SF

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;118(5):1858-66. [Abstract]

Ubiquitination of TRAF6 has been shown to play an important role in mediating RANK signaling for the stimulation of osteoclast (OC) formation, and lysine 63-linked polyubiquitin chains facilitate the association of TRAF6 with its target signaling factors, such as IKK. Here, the authors demonstrate that the expression level of a deubiquitinating enzyme, CYLD, is low in macrophages but is drastically upregulated by RANKL-induced osteoclastogenesis. CYLD negatively regulates RANK signaling by deubiquitinating TRAF6 and inhibiting downstream signaling. Deletion of CYLD in mice causes formation of enlarged and hypernucleated OCs, and is associated with severe osteoporosis. The adaptor protein p62 physically interacts at its C-terminal region with CYLD to promote the binding of CYLD with TRAF6. This is the first demonstration that a deubiquitinating enzyme is a crucial negative regulator of osteoclastogenesis. Further elucidation of the negative regulatory system of osteoclastogenesis by CYLD may suggest a new therapeutic approach. —TM

Reviews, Perspectives and Editorials

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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.