IBMS BoneKEy. 2009 June;6(6):194-199
http://www.bonekey-ibms.org/cgi/content/full/ibmske;6/6/194
doi: 10.1138/20090379

NOT TO BE MISSED

Clinical and Basic Research Papers – June 2009

Serge Ferrari, Editor-in-Chief
Ego Seeman, Clinical Editor
Hong-Wen Deng, Associate Editor
David G. Little, Associate Editor
Toshio Matsumoto, Associate Editor

Clinical Studies and Drug Effects

Eddleston A, Marenzana M, Moore AR, Stephens P, Muzylak M, Marshall D, Robinson MK. A short treatment with an antibody to sclerostin can inhibit bone loss in an ongoing model of colitis. *J Bone Miner Res*. 2009 May 6. [Epub ahead of print] [Abstract]

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*. 2009 Apr;24(4):578-88. [Abstract]

> *The literature on sclerostin antibody treatment is coming. It is important because sclerostin may be a profound stimulator of bone formation and inhibitor of bone resorption. The real test will come with studies in human subjects but here is a taste of things to come provided the best laid plans of mice and rats foretell the fate of primates. Eddleston et al. report that sclerostin antibody in mice reversed the decline of intrinsic and extrinsic mechanical properties. Markers of bone formation and resorption suggest stimulation of osteoblast activity and inhibition of osteoclast-mediated bone resorption. Li et al. administered the antibody to rats and reported increased bone formation on trabecular, periosteal, endocortical, and intracortical surfaces. Complete reversal of deficits induced by gonadectomy was reported with further increases in bone mass and strength greater than those in non-ovariectomized controls.* —ES

Fulciniti M, Tassone P, Hideshima T, Vallet S, Nanjappa P, Ettenberg SA, Shen Z, Patel N, Tai YT, Chauhan D, Mitsiades C, Prabhala R, Raje N, Anderson KC, Stover DR, Munshi NC. Anti-DKK1 mAb (BHQ880) as a potential therapeutic agent for multiple myeloma. *Blood*. 2009 May 5. [Epub ahead of print]

> *Decreased osteoblastic bone formation contributes to the devastating bone destruction in multiple myeloma (MM). The soluble Wnt inhibitor Dickkopf-1 (DKK1) is secreted from MM cells, inhibits osteoblastogenesis and plays a role in the formation of bone lesions in MM. The authors evaluated bone anabolic effects of a DKK1 neutralizing antibody (BHQ880) in MM. BHQ880 neutralized the negative effect of MM cells on osteoblastogenesis in vitro. BHQ880 treatment in vivo using a SCID-hu murine model of human MM increased osteoblast number, serum human osteocalcin levels and trabecular bone, with an inhibition of MM cell growth. Thus, DKK1 can be an important therapeutic target in MM to improve bone disease and inhibit MM growth.* —TM

Odvina CV, Levy S, Rao S, Zerwekh JE, Sudhaker Rao D. Unusual mid-shaft fractures during

long term bisphosphonate therapy. *Clin Endocrinol (Oxf)*. 2009 Mar 19. [Epub ahead of print] [Abstract]

Wang X, Erickson AM, Allen MR, Burr DB, Martin RB, Hazelwood SJ. Theoretical analysis of alendronate and risedronate effects on canine vertebral remodeling and microdamage. *J Biomech*. 2009 May 11;42(7):938-44. [Abstract]

> *Life may or may not imitate art. Remodeling is needed for damage repair but as remodeling balance between the volumes of bone formed and resorbed is negative, every time remodeling occurs bone is lost and structural damage occurs. The question is what is the net effect of suppressing remodeling with accumulation of matrix damage and preventing structural decay? Wang et al. suggest that inhibiting remodeling may result in accumulation of microdamage but the prevention of structural decay may override matrix damage in most cases, producing a net benefit. Odvina et al. report 13 patients with atraumatic mid-shaft fractures; 10 received alendronate and 3 received risedronate therapy.* —ES

Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, Papanastasiou P, Ferreira A, Hartl F, Fashola T, Mesenbrink P, Sambrook PN; HORIZON investigators. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2009 Apr 11;373(9671):1253-63. [Abstract]

> *In patients chronically receiving glucocorticoids (GCs), in this instance mostly for rheumatic diseases, a single infusion of zoledronate (5 mg) improved BMD at all sites significantly more than 5 mg of risedronate daily. Worsening RA was recorded in a small percentage of patients in each group. Of note, subjects in this study were expected to need GCs for at least 12 months. In practice, it should be remembered that the decrease in bone mass and increased fracture risk associated with GCs are at least partially reversible when GCs are stopped, whereas the effects of a single infusion of zoledronate on bone turnover may be maintained for longer than one year.* —SF

Genetics

Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, Yoon D, Lee MH, Kim DJ, Park M, Cha SH, Kim JW, Han BG, Min H, Ahn Y, Park MS, Han HR, Jang HY, Cho EY, Lee JE, Cho NH, Shin C, Park T, Park JW, Lee JK, Cardon L, Clarke G, McCarthy MI, Lee JY, Lee JK, Oh B, Kim HL. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. *Nat Genet*. 2009 May;41(5):527-34. [Abstract]

> *This is a genome-wide association study, performed in a very large Korean population, which aims to identify genetic factors influencing quantitative traits of biomedical importance. Two loci (7q31 and 7p14) influencing BMD were identified with consistent associations at the tibia and heel.* —HWD

Molecular and Cell Biology

Chang J, Wang Z, Tang E, Fan Z, McCauley L, Franceschi R, Guan K, Krebsbach PH, Wang CY. Inhibition of osteoblastic bone formation by nuclear factor-kappaB. *Nat Med*. 2009 May 17. [Epub ahead of print] [Abstract]

> *Using a dominant-negative mutant of IKK-γ (IKK-DN) and a superrepressor of IκBα driven by the OSE2 promoter of the osteocalcin gene (Bglap2), the authors demonstrate*

that inhibition of NF-κB in mature osteoblasts (OBs) increases trabecular BMD by enhancing OB function without affecting OB differentiation. Inhibition of NF-κB in mature OBs did not affect osteoclast activity. Mature OB-specific inhibition of NF-κB prevented ovariectomy-induced bone loss in adult Bglap2-IKK-DN mice. In Bglap2-IKK-DN OBs, Fra-1 expression was enhanced whereas the expression of other AP-1 family members, including FosB and DFosB, was not altered. The results suggest that targeting NF-κB can not only suppress bone resorption but also promote bone formation, and may provide a new modality of therapy for osteoporosis and inflammatory bone disorders. —TM

Kahn J, Shwartz Y, Blitz E, Krief S, Sharir A, Breitel DA, Rattenbach R, Relaix F, Maire P, Rountree RB, Kingsley DM, Zelzer E. Muscle contraction is necessary to maintain joint progenitor cell fate. *Dev Cell*. 2009 May;16(5):734-43. [Abstract]

Muscleless mice fail to develop proper joints, as in absence of contraction, and joint progenitor cells lose their normal sequence of differentiation and proliferation and instead differentiate into chondrocytes. This study further suggests that Wnt9a expression is lost and β-catenin signaling is reduced in joint-forming cells in the absence of muscle contraction. —SF

Moedder UI, Monroe DG, Fraser DG, Spelsberg TC, Rosen CJ, Gehin M, Chambon P, O'Malley BW, Khosla S. Skeletal consequences of deletion of steroid receptor coactivator-2(SRC-2)/transcription intermediary factor-2(TIF-2). *J Biol Chem*. 2009 May 7. [Epub ahead of print]

Bone loss and marrow fat gain, as observed in osteoporosis, may be largely explained by the activation of PPARγ, which inhibits osteoblastogenesis while promoting adipogenesis. Here it is shown that mice lacking the steroid receptor coactivator (SRC)-2 (TIF-2) have an increase in trabecular bone of 80% and a decrease in marrow fat of 50%, compared to wild type mice. Moreover MSCs from TIF-2 KO mice formed more mineralized bone nodules, rather than adipocytes, in the presence of the PPARγ agonist rosiglitazone. Hence, TIF-2 co-activation of PPARγ appears to have a predominant effect on its co-activation of the estrogen receptor (ER)-α. —SF

Pathophysiology

Schinke T, Schilling AF, Baranowsky A, Seitz S, Marshall RP, Linn T, Blaeker M, Huebner AK, Schulz A, Simon R, Gebauer M, Priemel M, Kornak U, Perkovic S, Barvencik F, Beil FT, Fattore AD, Frattini A, Streichert T, Pueschel K, Villa A, Debatin KM, Rueger JM, Teti A, Zustin J, Sauter G, Amling M. Impaired gastric acidification negatively affects calcium homeostasis and bone mass. *Nat Med*. 2009 May 17. [Epub ahead of print] [Abstract]

Osteoclast acidification defects lead to osteopetrosis, and in some cases to hypocalcemia and poor bone mineralization (osteomalacia/rickets). Through an elegant series of studies in humans and mice, it is shown here that impairment of bone resorption itself is necessary, but not sufficient, to explain the osteopetrorickets phenotype. Rather, Tcirg1 mutations also affect gastric acidification and thereby calcium absorption potentially, which together with the osteoclastic defect leads to the above abnormalities. —SF

Reviews, Perspectives and Editorials

Farquhar C, Marjoribanks J, Lethaby A, Suckling JA, Lamberts Q. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2009 Apr 15;(2):CD004143. [Abstract]

Marini JC. Bone: Use of bisphosphonates in children-proceed with caution. *Nat Rev Endocrinol*. 2009 May;5(5):241-3. [Abstract]

Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws--2009 update. *J Oral Maxillofac Surg*. 2009 May;67(5 Suppl):2-12. [Info]

Other Studies of Potential Interest

Anastasilakis AD, Bhansali A, Ahluwalia J, Chanukya GV, Behera A, Dutta P. No difference between strontium ranelate (SR) and calcium/vitamin D on bone turnover markers in women with established osteoporosis previously treated with teriparatide: a randomized controlled trial. *Clin Endocrinol (Oxf)*. 2009 Apr;70(4):522-6. [Abstract]

Biosse-Duplan M, Baroukh B, Dy M, de Vernejoul MC, Saffar JL. Histamine promotes osteoclastogenesis through the differential expression of histamine receptors on osteoclasts and osteoblasts. *Am J Pathol*. 2009 Apr;174(4):1426-34. [Abstract]

Bolognese M, Krege JH, Utian WH, Feldman R, Broy S, Meats DL, Alam J, Lakshmanan M, Omizo M. Effects of arzoxifene on bone mineral density and endometrium in postmenopausal women with normal or low bone mass. *J Clin Endocrinol Metab*. 2009 Apr 7. [Epub ahead of print] [Abstract]

Cawthon PM, Ewing SK, McCulloch CE, Ensrud KE, Cauley JA, Cummings SR, Orwoll ES; for the Osteoporotic Fractures in Men (MrOS) Research Group. Loss of hip bone mineral density in older men: The Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res*. 2009 May 6. [Epub ahead of print] [Abstract]

de Freitas PH, Li M, Ninomiya T, Nakamura M, Ubaidus S, Oda K, Udagawa N, Maeda T, Takagi R, Amizuka N. Intermittent parathyroid hormone administration stimulates preosteoblastic proliferation without leading to enhanced bone formation in osteoclast-less c-fos(-/-) mice. *J Bone Miner Res*. 2009 May 6. [Epub ahead of print] [Abstract]

Ebert R, Zeck S, Krug R, Meissner-Weigl J, Schneider D, Seefried L, Eulert J, Jakob F. Pulse treatment with zoledronic acid causes sustained commitment of bone marrow derived mesenchymal stem cells for osteogenic differentiation. *Bone*. 2009 May;44(5):858-64. [Abstract]

Lang DH, Conroy DE, Lionikas A, Mack HA, Larsson L, Vogler GP, Vandenbergh DJ, Blizard DA, McClearn GE, Sharkey NA. Bone, muscle and physical activity: structural equation modeling of relationships and genetic influence with age. *J Bone Miner Res*. 2009 May 6. [Epub ahead of print] [Abstract]

Leder BZ, Neer RM, Wyland JJ, Lee H, Burnett-Bowie SA, Finkelstein JS. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. *J Clin Endocrinol Metab*. 2009 May 12. [Epub ahead of print] [Abstract]

Lin EA, Kong L, Bai XH, Luan Y, Liu CJ. miR-199a, a bone morphogenic protein 2-responsive microRNA, regulates chondrogenesis via direct targeting to Smad1. *J Biol Chem*. 2009 Apr 24;284(17):11326-35. [Abstract] [Full Text]

Liu J, Wang S, Zhang P, Said-Al-Naief N, Michalek SM, Feng X. Molecular mechanism of the bifunctional role of lipopolysaccharide in osteoclastogenesis. *J Biol Chem*. 2009 May 1;284(18):12512-23. [Abstract] [Full Text]

McMichael BK, Wysolmerski RB, Lee BS. Regulated proteolysis of nonmuscle myosin IIA stimulates osteoclast fusion. *J Biol Chem*. 2009 May 1;284(18):12266-75. [Abstract] [Full Text]

Mullin BH, Prince RL, Mamotte C, Spector TD, Hart DJ, Dudbridge F, Wilson SG. Further genetic evidence suggesting a role for the RhoGTPase-RhoGEF pathway in osteoporosis. *Bone*. 2009 May 7. [Epub ahead of print] [Abstract]

Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, Sebring N, Troendle JF, Nelson LM. Bone mineral density in estrogen deficient young women. *J Clin Endocrinol Metab*. 2009 Apr 28. [Epub ahead of print] [Abstract]

Ringe JD, Möller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. *Rheumatol Int*. 2009 May 9. [Epub ahead of print] [Abstract]

Sheng MH, Amoui M, Stiffel V, Srivastava AK, Wergedal JE, Lau KH. Targeted transgenic expression of an osteoclastic transmembrane protein-tyrosine phosphatase in cells of osteoclastic lineage increases bone resorption and bone loss in male young adult mice. *J Biol Chem*. 2009 Apr 24;284(17):11531-45. [Abstract] [Full Text]

Smink JJ, Bégay V, Schoenmaker T, Sterneck E, de Vries TJ, Leutz A. Transcription factor C/EBPbeta isoform ratio regulates osteoclastogenesis through MafB. *EMBO J*. 2009 May 14. [Epub ahead of print] [Abstract]

Veverka V, Henry AJ, Slocombe PM, Ventom A, Mulloy B, Muskett FW, Muzylak M, Greenslade K, Moore A, Zhang L, Gong J, Qian X, Paszty C, Taylor RJ, Robinson MK, Carr MD. Characterization of the structural features and interactions of sclerostin: molecular insight into a key regulator of Wnt-mediated bone formation. *J Biol Chem*. 2009 Apr 17;284(16):10890-900. [Abstract] [Full Text]

Yerges LM, Klei L, Cauley JA, Roeder K, Kammerer CM, Moffett SP, Ensrud KE, Nestlerode CS, Marshall LM, Hoffman AR, Lewis C, Lang TF, Barrett-Connor E, Ferrell RE, Orwoll ES, Zmuda JM; for the MrOS Research Group. A high-density association study of 383 candidate genes for volumetric bone density at the femoral neck and lumbar spine among older men. *J Bone Miner Res*. 2009 May 19. [Epub ahead of print] [Abstract]

Zhang S, Liu C, Huang P, Zhou S, Ren J, Kitamura Y, Tang P, Bi Z, Gao B. The affinity of human RANK binding to its ligand RANKL. *Arch Biochem Biophys*. 2009 May 3. [Epub ahead of print] [Abstract]

Zhong Y, Armbrecht HJ, Christakos S. Calcitonin, a regulator of the 25-hydroxyvitamin D3 1alpha-hydroxylase gene. *J Biol Chem*. 2009 Apr 24;284(17):11059-69. [Abstract] [Full Text]

IBMS BoneKEy. 2009 June;6(6):194-199
http://www.bonekey-ibms.org/cgi/content/full/ibmske;6/6/194
doi: 10.1138/20090379

Zou W, Reeve JL, Zhao H, Ross FP, Teitelbaum SL. Syk tyrosine 317 negatively regulates osteoclast function via the E3 ligase activity of cbl. *J Biol Chem*. 2009 May 6. [Epub ahead of print]

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.