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NOT TO BE MISSED

Clinical and Basic Research Papers – August 2011

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Clinical Studies and Drug Effects

Fitzpatrick LA, Dabrowski CE, Cicconetti G, Gordon DN, Papapoulos S, Bone HG 3rd, Bilezikian JP. The effects of ronacaleret, a calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density. *J Clin Endocrinol Metab*. 2011 May 18. [Epub ahead of print] [Abstract]

> *569 postmenopausal women with low BMD were treated with either 20 μg subcutaneous teriparatide daily, 100, 200, 300, or 400 mg oral ronacaleret daily, 70 mg alendronate once weekly, or placebo. Ronacaleret increased spine BMD at 12 months (0.3-1.6%), less than teriparatide (9.1%) or alendronate (4.5%). Total hip, femoral neck, and trochanter BMD decreased with ronacaleret but increased with teriparatide and alendronate. Remodeling markers increased with ronacaleret and teriparatide and decreased with alendronate. These data seem to be ruining a good idea; endogenous PTH may be doing more harm than good when osteoclasts are around.* —ES

John MR, Widler L, Gamse R, Buhl T, Seuwen K, Breitenstein W, Bruin GJ, Belleli R, Klickstein LB, Kneissel M. ATF936, a novel oral calcilytic, increases bone mineral density in rats and transiently releases parathyroid hormone in humans. *Bone*. 2011 Aug;49(2):233-41. [Abstract]

> *The search for an effective calcilytic to treat osteoporosis is still ongoing. The compound investigated here holds new promise since oral administration to aged rats dose-dependently improved bone mass, trabecular and cortical structure at the proximal diaphysis, but increased serum calcium levels; it induced short serum PTH peaks in humans without post-dose hypercalcemia, similar to 20 μg subcutaneous teriparatide.* —SF

Rubin M, Dempster D, Sliney J, Zhou H, Nickolas T, Stein E, Dworakowski E, Dellabadia M, Ives R, McMahon D, Zhang C, Silverberg S, Shane E, Cremers S, Bilezikian J. PTH(1-84) administration reverses abnormal bone remodeling dynamics and structure in hypoparathyroidism. *J Bone Miner Res*. 2011 Jul 6. [Epub ahead of print] [Abstract]

Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L; the hypoparathyroid study group. The effect of adding PTH (1-84) to conventional treatment of hypoparathyroidism - A randomized, placebo controlled study. *J Bone Miner Res*. 2011 Jul 19. [Epub ahead of print] [Abstract]

> *These two separate studies investigated the effects of intact PTH administration in patients with hypoparathyroidism, in addition to standard vitamin D, calcium and*

calcitriol treatment. In the bone biopsy study by Rubin et al., PTH(1-84) 100 μg subcutaneously every other day induced a marked increase in bone-forming and remodeling indices at 3 months, 1 and 2 years, with related changes in microstructure, namely increased trabecular number and cortical porosity. Consistent with these results, in the Sikjaer et al. study, twice-daily PTH(1-84) 100 μg markedly increased biochemical markers of bone turnover, decreased aBMD at the spine and hip, and maintained normal serum calcium levels while decreasing calcium and vitamin D dosing. The true clinical benefit of intact PTH in this setting remains to be established. —SF

Shapses SA, Kendler DL, Robson R, Hansen KE, Sherrell RM, Field MP, Woolf E, Berd Y, Mantz AM, Santora AC 2nd. Effect of alendronate and vitamin D(3) on fractional calcium absorption in a double-blind, randomized, placebo-controlled trial in postmenopausal osteoporotic women. *J Bone Miner Res*. 2011 Aug;26(8):1836-44. [Abstract]

This small, randomized controlled trial of weekly alendronate (ALN) + vitamin D (2800 IU) shows some intriguing results, namely that compared to placebo, ALN + low-dose vitamin D not only substantially increased 25OHD levels (+8.7 ng/ml) and fractional calcium absorption (+7% absolute increase) within one month, but also increased 1,25 dihydroxyvitamin D_3 and serum PTH levels by nearly 30%. Hence vitamin D supplements with concomitant anti-resorptive therapy leading to a secondary rise in serum PTH could synergize to increase 1,25 dihydroxyvitamin D_3 and calcium absorption. If that is true, ALN + D could be more than just a convenient combination, but also a true pharmacological principle. Too bad vitamin D-alone and ALN-alone groups were not included. —SF

Silverman SL, Chines AA, Kendler DL, Kung AW, Teglbjærg CS, Felsenberg D, Mairon N, Constantine GD, Adachi JD; for the Bazedoxifene Study Group. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. *Osteoporos Int*. 2011 Jul 21. [Epub ahead of print] [Abstract]

Continued treatment with bazedoxifene (BZX) for 5 years (20 mg or 40 to 20 mg after 3 years) in 4,216 women with osteoporosis resulted in a continuous decrease in morphometric vertebral fracture incidence (-35 to -40% vs. placebo at 5 yrs.). Treating 927 subjects with BZX 20 mg in years 4 and 5 prevented new vertebral fractures in 6 of them compared to placebo. The incidence of non-vertebral and hip (<1%) fractures was similar in treated and placebo groups overall. —SF

Cancer and Bone

Fradet A, Sorel H, Bouazza L, Goehrig D, Depalle B, Bellahcene A, Castronovo V, Follet H, Descotes F, Aubin J, Clezardin P, Bonnelye E. Dual function of ERRalpha in breast cancer and bone metastasis formation: implication of VEGF and osteoprotegerin. *Cancer Res*. 2011 Jul 6. [Epub ahead of print] [Abstract]

The estrogen receptor-related receptor alpha (ERRα) has been implicated in breast cancer and bone development. In this study, the authors have shown that ERRα plays a dual role in breast cancer progression: it upregulates the production of the angiogenic growth factor VEGF and the osteoclastogenesis inhibitor OPG by neoplastic cells, thereby promoting the vascularization of primary breast tumors, but decreasing metastatic growth of osteolytic lesions in bone. —SF

Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, Morrow M, Leitch AM, Hunt KK, McCall LM, Abati A, Cote R. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA*. 2011 Jul 27;306(4):385-93. [Abstract]

> *The aim of this study was to determine the association between survival and metastases detected by immunochemical staining of sentinel lymph nodes (SLNs) and bone marrow specimens from patients with early-stage breast cancer in a prospective observational study (median follow-up of 6.3 years). Of 3,326 SLN specimens examined by immunohistochemistry, 349 (10.5%) were positive for tumors. Of 3,413 bone marrow specimens examined by immunocytochemistry, 104 (3.0%) were positive for tumors. Immunohistochemical evidence of SLN metastasis was not associated with overall survival, whereas occult bone marrow metastasis was associated with a 94% increase in the risk of mortality (HR = 1.94; 95% CI, 1.02-3.67; P = .04)*. —PC

Kunita A, Kashima TG, Ohazama A, Grigoriadis AE, Fukayama M. Podoplanin is regulated by AP-1 and promotes platelet aggregation and cell migration in osteosarcoma. *Am J Pathol*. 2011 Aug;179(2):1041-9. [Abstract]

> *In this study, podoplanin (a type-I transmembrane sialomucin-like protein) was found to be highly expressed in metastatic osteosarcomas, suggesting it could be a candidate molecule for therapeutic targeting.* —PC

Morgan GJ, Child JA, Gregory WM, Szubert AJ, Cocks K, Bell SE, Navarro-Coy N, Drayson MT, Owen RG, Feyler S, Ashcroft AJ, Ross FM, Byrne J, Roddie H, Rudin C, Cook G, Jackson GH, Wu P, Davies FE; on behalf of the National Cancer Research Institute Haematological Oncology Clinical Studies Group. Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. *Lancet Oncol*. 2011 Aug;12(8):743-752. [Abstract]

> *1,960 patients with newly diagnosed multiple myeloma received zoledronate (n = 981) or clodronate (n = 979). The early use of zoledronate was better than clodronate for prevention of skeletal-related events (HR = 0.74 ; 95% CI, 0.62-0.87 ; P = 0.0004).* —PC

Oskarsson T, Acharyya S, Zhang XH, Vanharanta S, Tavazoie SF, Morris PG, Downey RJ, Manova-Todorova K, Brogi E, Massagué J. Breast cancer cells produce tenascin C as a metastatic niche component to colonize the lungs. *Nat Med*. 2011 Jun 26;17(7):867-74. [Abstract]

> *The authors find that the expression of tenascin C (TNC) in breast cancer cells is associated with the aggressiveness of pulmonary and bone metastases. Cancer cell-derived TNC is essential for the outgrowth of micrometastases. This extracellular matrix component enhances WNT and NOTCH signaling activity in cancer cells, promoting cell survival. These findings highlight the importance of tumor-derived TNC in the formation of the metastatic niche.* —PC

Genetics

The Australo-Anglo-American Spondyloarthritis Consortium (TASC), the Wellcome Trust Case Control Consortium 2 (WTCCC2), Evans DM, Spencer CC, Pointon JJ, et al. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat Genet*. 2011 Jul 10;43(8):761-7. [Abstract]

> *Matthew Brown and colleagues report results of a GWAS of ankylosing spondylitis,*

which is a common form of inflammatory arthritis predominantly affecting the spine and pelvis. They identified three new risk variants in the RUNX3, LTBR-TNFRSF1A, and IL12B regions, and four loci at PTGER4, TBKBP1, ANTXR2 and CARD9 that show suggestive association. Notably, PTGER4 – prostaglandin E receptor 4 – is a component of the "mechanostat" anabolic bone response to physical stress, found at the site of entheses (insertion of tendons and ligaments into bone). The paper also reports an interaction between the ERAP1 and HLA-B27 genes. —DK

Dolmans GH, Werker PM, Hennies HC, Furniss D, Festen EA, Franke L, Becker K, van der Vlies P, Wolffenbuttel BH, Tinschert S, Toliat MR, Nothnagel M, Franke A, Klopp N, Wichmann HE, Nürnberg P, Giele H, Ophoff RA, Wijmenga C; Dutch Dupuytren Study Group; German Dupuytren Study Group; LifeLines Cohort Study; BSSH-GODD Consortium. Wnt signaling and Dupuytren's disease. *N Engl J Med*. 2011 Jul 28;365(4):307-17. [Abstract]

Dupuytren's disease is a fibromatosis of the flexors of fingers that leads to flexion contractures. Very little is known about the heritability of this disease, despite some reports of familial aggregation. This paper reports a GWAS of 960 Dutch affected persons and 3,117 controls; 35 SNPs most strongly associated with Dupuytren's disease were further taken to replication in three additional case/control series from Germany, the United Kingdom, and the Netherlands. Six of the 9 identified loci contained genes known to be involved in the Wnt-signaling pathway, including WNT4, WNT2, WNT7B, and RSPO2. The latter gene encodes an R-spondin (Rspo), a member of the family interacting with frizzled receptors and LRP5/6 to induce β-catenin signaling; Rspo also competes with dickkopf (DKK) protein. Moreover, Rspo2 expression is required for Wnt11-mediated osteoblast maturation, thus making an interesting connection with bone biology. —DK

Mineur YS, Abizaid A, Rao Y, Salas R, DiLeone RJ, Gündisch D, Diano S, De Biasi M, Horvath TL, Gao XB, Picciotto MR. Nicotine decreases food intake through activation of POMC neurons. *Science*. 2011 Jun 10;332(6035):1330-2. [Abstract] [Full Text]

Rothem DE, Rothem L, Dahan A, Eliakim R, Soudry M. Nicotinic modulation of gene expression in osteoblast cells, MG-63. *Bone*. 2011 Apr 1;48(4):903-9. [Abstract]

When the Russian czar Peter the Great advocated for smoking tobacco, he appealed to the benefit of decreasing appetite. He could not possibly know about the beneficial effect of nicotine on bone health. Indeed, Mineur et al. find that activation of hypothalamic $\alpha 3\beta 4$ nicotinic acetylcholine receptors leads to activation of pro-opiomelanocortin neurons, which together with subsequent activation of melanocortin 4 receptors were critical for nicotinic-induced decreases in food intake in mice. Rothem et al. performed whole human genome gene expression microarray on RNA samples from osteoblast-like cells, MG-63, exposed to 100 μM nicotine, to identify nicotine-regulated genes. Quantitative real-time RT PCR analysis confirmed altered expression in 7 genes that promote osteoblast proliferation and/or anti-apoptosis processes, including cyclin D1, endothelin 1, BCL2-associated X protein (BAX), caveolin 1, and JUN. Furthermore, their results suggest that nicotinic stimulation of the same $\alpha 3$ nicotinic acetylcholine receptor in human osteoblasts is required to regulate those genes. —DK

Yang N, Schindeler A, McDonald MM, Seto JT, Houweling PJ, Lek M, Hogarth M, Morse AR, Raftery JM, Balasuriya D, Macarthur DG, Berman Y, Eisman JA, Nguyen TV, Center JR, Prince RL, Wilson SG, Zhu K, Little DG, North KN. α-Actinin-3 deficiency is associated with reduced bone mass in human and mouse. *Bone*. 2011 Jul 21. [Epub ahead of print] [Abstract]

Actinin-3 (ACTN3 gene) is expressed in muscle and its deficiency is detrimental to sprint and power performance in humans. Here it is shown that Actinin-3 is also expressed in osteoblasts; its deletion in mice leads to a low bone mass phenotype with decreased bone formation; and a stop polymorphism (R577X) in humans is associated with lower aBMD. A nice example of functional genetics from humans to mice and back to humans. —SF

Bone Modeling, Remodeling, and Repair

Alexander KA, Chang MK, Maylin ER, Kohler T, Müller R, Wu AC, Van Rooijen N, Sweet MJ, Hume DA, Raggatt LJ, Pettit AR. Osteal macrophages promote in vivo intramembranous bone healing in a mouse tibial injury model. *J Bone Miner Res*. 2011 Jul;26(7):1517-32. [Abstract]

This is the latest work implicating osteal macrophages (osteomacs) as important elements in the anabolic response to injury. When osteomacs were depleted in the Mafia transgenic model or via clodronate-containing liposomes, healing was adversely affected, whereas OPG treatment (inhibiting osteoclastogenesis but not affecting osteomacs) had no effect on intramembranous bone formation. —DGL

Deng M, Zhang B, Wang K, Liu F, Xiao H, Zhao J, Liu P, Li Y, Lin F, Wang Y. Mechano growth factor E peptide promotes osteoblasts proliferation and bone-defect healing in rabbits. *Int Orthop*. 2011 Jul;35(7):1099-106. [Abstract]

Mechano growth factor (MGF) is a splice variant of IGF apparently produced in situations of tissue damage. It has a unique C-terminal peptide (termed E peptide) that was active in MC3T3 proliferation. In vivo, a 5-mm segmental bone defect in rabbit radii treated with MGF-Ct24E by daily intralesion injection improved bone formation. Peptides are cheaper to produce than proteins; the current finding might enable a novel biologic treatment. —DGL

Doi Y, Miyazaki M, Yoshiiwa T, Hara K, Kataoka M, Tsumura H. Manipulation of the anabolic and catabolic responses with BMP-2 and zoledronic acid in a rat femoral fracture model. *Bone*. 2011 Jul 14. [Epub ahead of print] [Abstract]

Belfrage O, Flivik G, Sundberg M, Kesteris U, Tägil M. Local treatment of cancellous bone grafts with BMP-7 and zoledronate increases both the bone formation rate and bone density: a bone chamber study in rats. *Acta Orthop*. 2011 Apr;82(2):228-33. [Abstract]

Schindeler A, Birke O, Yu NY, Morse A, Ruys A, Baldock PA, Little DG. Distal tibial fracture repair in a neurofibromatosis type 1-deficient mouse treated with recombinant bone morphogenetic protein and a bisphosphonate. *J Bone Joint Surg Br*. 2011 Aug;93(8):1134-9. [Abstract]

3 related papers from different groups. Each tests the combination of BMPs and bisphosphonates (BPs). In the fracture healing study by Doi et al., union was advanced and mechanical properties were best in the combined BMP/BP group. This was also the case in the bone chamber study by Belfrage et al., where the BP zoledronic acid was delivered locally. In the final study, in a model of pathologic fracture healing in NF1 heterozygous mice, combined BMP and zoledronic acid treatment resulted in better union than BMP alone. Combining anabolic and anti-catabolic agents is a powerful emerging strategy. —SF

Li X, Grisanti M, Fan W, Asuncion FJ, Tan HL, Dwyer D, Han CY, Yu L, Lee J, Lee E, Barrero

M, Kurimoto P, Niu QT, Geng Z, Winters A, Horan T, Steavenson S, Jacobsen F, Chen Q, Haldankar R, Lavallee J, Tipton B, Daris M, Sheng J, Lu HS, Daris K, Deshpande R, Valente EG, Salimi-Moosavi H, Kostenuik PJ, Li J, Liu M, Li C, Lacey DL, Simonet WS, Ke HZ, Babij P, Stolina M, Ominsky MS, Richards WG. Dickkopf-1 regulates bone formation in young growing rodents and upon traumatic injury. *J Bone Miner Res*. 2011 Jul 19. [Epub ahead of print] [Abstract]

> *This is an Amgen group paper on the effects of antibody to Dkk1 that blocked binding to both LRP6 and Kremen2. Treatment with Dkk1-Ab in growing mice and rats increased BMD via increases in bone formation. However, unlike Scl-Ab, treatment of adult ovariectomized rats did not appreciably impact bone, an effect that was associated with decreased Dkk1 expression in the serum and bone of older rats. In adult bone Dkk1 does play a role in fracture healing, where it is again expressed in the adult animal. Callus density, strength and stiffness were improved with Dkk1 antibody, with no effect on the contralateral limb. Dkk1 is important in growing bones, the response to trauma and also in bone pathologies such as myeloma where it is expressed, but does not appear to be a potent factor in adult bone homeostasis based on these data.* —DGL

Shinohara K, Greenfield S, Pan H, Vasanji A, Kumagai K, Midura RJ, Kiedrowski M, Penn MS, Muschler GF. Stromal cell-derived factor-1 and monocyte chemotactic protein-3 improve recruitment of osteogenic cells into sites of musculoskeletal repair. *J Orthop Res*. 2011 Jul;29(7):1064-9. [Abstract]

> *In parabiotic experiments between GFP and WT mice, implants containing cells secreting stromal cell-derived factor-1 (SDF-1) or monocyte chemotactic protein-3 (MCP-3) increased homing from the GFP mouse circulation to the WT mouse. These factors may prove useful in tissue engineering.* —DGL

Molecular and Cell Biology

Chen H, Gilbert LC, Lu X, Liu Z, You S, Weitzmann MN, Nanes MS, Adams J. A new regulator of osteoclastogenesis: Estrogen response element binding protein in bone. *J Bone Miner Res*. 2011 Jul 19. [Epub ahead of print] [Abstract]

Syed FA, Fraser DG, Monroe DG, Khosla S. Distinct effects of loss of classical estrogen receptor signaling versus complete deletion of estrogen receptor alpha on bone. *Bone*. 2011 Aug;49(2):208-16. [Abstract]

> *Estrogen through its nuclear receptors (ERs) and a host of co-regulatory elements is the key regulator of the molecular programming of osteoclastogenesis. The first in vitro study reveals that estrogen response element binding protein (ERE-BP) acts as an antagonist of estrogen/ER binding to EREs in osteoblast progenitors, and thereby upregulates RANKL expression, while in osteoclasts it promotes RANK expression. The second study goes further by analyzing the role of ER signaling independent of its binding to EREs. Analysis of a knock-in mouse expressing an ER mutant that is defective in ERE activation (NERK1) showed that the skeletal phenotype of low aBMD, decreased cortical bone, but increased BV/TV was worse in NERK1 than ESR1 (ERα) KO mice. Indices of bone formation were further reduced in NERK1 mice, arguing for an inhibitory effect of non-classical estrogen effects on bone, that is, in the absence of ERE activation.* —SF

Levaot N, Simoncic PD, Dimitriou ID, Scotter A, La Rose J, Ng AH, Willett TL, Wang CJ, Janmohamed S, Grynpas M, Reichenberger E, Rottapel R. 3BP2-deficient mice are osteoporotic

with impaired osteoblast and osteoclast functions. *J Clin Invest*. 2011 Aug 1;121(8):3244-57. [Abstract]

> *3BP2 is encoded by the SH3-domain binding protein 2 (Sh3bp2) gene, and binds to Src family kinases. Gain-of-function mutation in the Sh3bp2 gene is associated with the majority of cherubism patients, causing cystic bone lesions with activated osteoclasts that lead to craniofacial abnormalities. The authors show that Sh3bp2(-/-) mice developed osteoporosis with reduced bone formation and impaired bone resorption. The tyrosine kinase Abl was not activated in Sh3bp2(-/-) osteoblasts, which failed to mature and form mineralized nodules in vitro. Src was not activated in Sh3bp2(-/-) osteoclasts, which spread poorly and were unable to resorb dentine matrix in vitro. Thus, 3BP2 is required for both bone resorption and formation, by acting as an adaptor protein for Abl in osteoblasts and Src in osteoclasts.* —TM

van der Eerden BC, Weissgerber P, Fratzl-Zelman N, Olausson J, Hoenderop JG, Schreuders-Koedam M, Eijken M, Roschger P, de Vries TJ, Chiba H, Klaushofer K, Flockerzi V, Bindels RJ, Freichel M, van Leeuwen JP. The transient receptor potential channel TRPV6 is dynamically expressed in bone cells but is not crucial for bone mineralization in mice. *J Cell Physiol*. 2011 Jul 5. [Epub ahead of print] [Abstract]

> *Previous analysis of the bone phenotype of TRPV6 (the major intestinal calcium channel) KO mice showed that bone mineralization in these mice was only impaired on a low-calcium diet. Since TRPV6 is also weakly expressed in some bone cells, it remained unclear whether the latter observation was only due to poor intestinal calcium absorption and/or impaired mineralizing function in osteoblasts. The present study characterizes the expression of TRPV6 in osteoblasts and osteoclasts and demonstrates that mineralization in vitro and in vivo is not altered by TRPV6 expression.* —SF

Wang W, Nyman JS, Ono K, Stevenson DA, Yang X, Elefteriou F. Mice lacking Nf1 in osteochondroprogenitor cells display skeletal dysplasia similar to patients with neurofibromatosis type I. *Hum Mol Genet*. 2011 Jul 14. [Epub ahead of print] [Abstract]

> *The authors utilized the mouse Col2α1-Cre promoter that is active not only in chondrocytes but also in osteoprogenitors to conditionally delete the Nf1 gene in osteochondroprogenitor cells. These mice recapitulated the skeletal abnormalities of NF1 patients, with progressive scoliosis and kyphosis, tibial bowing, and skull and anterior chest wall malformation. The Ras-ERK pathway was constitutively activated in BMSCs of these mice, and blockade of Ras activation via inhibition of Ras prenylation by lovastatin during embryonic development attenuated the increased cortical porosity in mutant mice. These data suggest that activation of the Ras-ERK pathway by Nf1 loss-of-function in osteochondroprogenitors is responsible for the vertebral and tibia lesions in NF1 patients.* —TM

Woo SM, Rosser J, Dusevich V, Kalajzic I, Bonewald LF. Cell line IDG-SW3 replicates osteoblast-to-late-osteocyte differentiation in vitro and accelerates bone formation in vivo. *J Bone Miner Res*. 2011 Jul 6. [Epub ahead of print] [Abstract]

> *The authors crossed mice carrying a Dmp1 promoter-driven GFP with the Immortomouse expressing a thermolabile SV40 large T-antigen regulated by IFN-γ, and generated a clonal cell line, IDG-SW3, from long bone chips of these mice. These cells can be expanded at 33°C in the presence of IFN-γ and then differentiated at 37°C in the absence of IFN-γ. IDG-SW3 cells are Dmp1-GFP-positive and T-antigen-negative under osteogenic conditions. They differentiate into osteoblasts,*

early osteocytes that express E11/gp38, Dmp1, MEPE, and Phex, and late osteocytes that develop a dendritic morphology and express SOST/sclerostin and FGF23. When 3D cultures are implanted in calvarial defects in vivo, they accelerate bone healing. This cell line should be of great use for studying osteoblast-to-osteocyte transition and osteocyte biology. —TM

Health Economics

Blume SW, Curtis JR. Medical costs of osteoporosis in the elderly Medicare population. *Osteoporos Int*. 2011 Jun;22(6):1835-44. [Abstract]

A cross-sectional estimate of cost was made in a random sample of 12,700 Medicare recipients. Three cohorts aged 65 or over were defined: patients experiencing a fracture, patients with a diagnosis or self-report for osteoporosis or past hip fracture, and controls. Of 30.2 million Medicare recipients in 2002, 1.6 million (5%) were treated for a fracture and 7.2 million (24%) had osteoporosis without a fracture. The estimated effect of fractures on annual medical cost in the US was $14 billion. Half of the non-fracture osteoporosis patients received drug treatment, averaging $500 per treated patient or $2 billion nationwide. The annual cost of osteoporosis and fractures in the US elderly was estimated at $16 billion using a national 2002 population-based sample. —ES

Reviews, Perspectives and Editorials

Histing T, Garcia P, Holstein JH, Klein M, Matthys R, Nuetzi R, Steck R, Laschke MW, Wehner T, Bindl R, Recknagel S, Stuermer EK, Vollmar B, Wildemann B, Lienau J, Willie B, Peters A, Ignatius A, Pohlemann T, Claes L, Menger MD. Small animal bone healing models: Standards, tips, and pitfalls results of a consensus meeting. *Bone*. 2011 Jul 19. [Epub ahead of print] [Abstract]

Niemeier A, Schinke T, Heeren J, Amling M. The role of apolipoprotein E in bone metabolism. *Bone*. 2011 Jul 23. [Epub ahead of print] [Abstract]

Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med*. 2011 Jul 7;365(1):62-70. [Info]

Other Studies of Potential Interest

Bishop KA, Coy HM, Nerenz RD, Meyer MB, Pike JW. Mouse Rankl expression is regulated in T cells by c-Fos through a cluster of distal regulatory enhancers designated the T cell control region. *J Biol Chem*. 2011 Jun 10;286(23):20880-91. [Abstract] [Full Text]

Bragdon B, Thinakaran S, Moseychuk O, Gurski L, Bonor J, Price C, Wang L, Beamer WG, Nohe A. Casein kinase 2 regulates in vivo bone formation through its interaction with bone morphogenetic protein receptor type Ia. *Bone*. 2011 Jul 14. [Epub ahead of print] [Abstract]

Brennan SL, Pasco JA, Cicuttini FM, Henry MJ, Kotowicz MA, Nicholson GC, Wluka AE. Bone mineral density is cross sectionally associated with cartilage volume in healthy, asymptomatic adult females: Geelong Osteoporosis Study. *Bone*. 2011 Jun 30. [Epub ahead of print] [Abstract]

Brown JP, Dempster DW, Ding B, Dent-Acosta R, San Martin J, Grauer A, Wagman RB, Zanchetta J. Bone remodeling in postmenopausal women who discontinued denosumab treatment: Off-treatment biopsy study. *J Bone Miner Res*. 2011 Jul 6. [Epub ahead of print]

[Abstract]

de Paula FJ, Dick-de-Paula I, Bornstein S, Rostama B, Le P, Lotinun S, Baron R, Rosen CJ. VDR haploinsufficiency impacts body composition and skeletal acquisition in a gender-specific manner. *Calcif Tissue Int*. 2011 Jun 3. [Epub ahead of print] [Abstract]

Deng FY, Lei SF, Chen XD, Tan LJ, Zhu XZ, Deng HW. An integrative study ascertained SOD2 as a susceptibility gene for osteoporosis in Chinese. *J Bone Miner Res*. 2011 Jul 19. [Epub ahead of print] [Abstract]

Di Martino MT, Arbitrio M, Guzzi PH, Leone E, Baudi F, Piro E, Prantera T, Cucinotto I, Calimeri T, Rossi M, Veltri P, Cannataro M, Tagliaferri P, Tassone P. A peroxisome proliferator-activated receptor gamma (PPARG) polymorphism is associated with zoledronic acid-related osteonecrosis of the jaw in multiple myeloma patients: analysis by DMET microarray profiling. *Br J Haematol*. 2011 Aug;154(4):529-33. [Abstract]

Faensen B, Wildemann B, Hain C, Höhne J, Funke Y, Plank C, Stemberger A, Schmidmaier G. Local application of BMP-2 specific plasmids in fibrin glue does not promote implant fixation. *BMC Musculoskelet Disord*. 2011 Jul 15;12(1):163. [Abstract]

Granero-Moltó F, Myers TJ, Weis JA, Longobardi L, Li T, Yan Y, Case N, Rubin J, Spagnoli A. Mesenchymal stem cells expressing insulin-like growth factor-I (MSC^{IGF}) promote fracture healing and restore new bone formation in Irs1 knock-out mice: analyses of MSC^{IGF} autocrine and paracrine regenerative effects. *Stem Cells*. 2011 Jul 22. [Epub ahead of print] [Abstract]

Gravenstein KS, Napora JK, Short RG, Ramachandran R, Carlson OD, Metter EJ, Ferrucci L, Egan JM, Chia CW. Cross-sectional evidence of a signaling pathway from bone homeostasis to glucose metabolism. *J Clin Endocrinol Metab*. 2011 Jun;96(6):E884-90. [Abstract] [Full Text]

Guggenbuhl P, Fergelot P, Doyard M, Libouban H, Roth MP, Gallois Y, Chalès G, Loréal O, Chappard D. Bone status in a mouse model of genetic hemochromatosis. *Osteoporos Int*. 2011 Aug;22(8):2313-9. [Abstract]

Inose H, Zhou B, Yadav VK, Guo XE, Karsenty G, Ducy P. Efficacy of serotonin inhibition in mouse models of bone loss. *J Bone Miner Res*. 2011 May 23. [Epub ahead of print] [Abstract]

Kim EK, Lim S, Park JM, Seo JK, Kim JH, Kim KT, Ryu SH, Suh PG. Human mesenchymal stem cell differentiation to the osteogenic or adipogenic lineage is regulated by AMP-activated protein kinase. *J Cell Physiol*. 2011 Jun 15. [Epub ahead of print] [Abstract]

Lin GL, Hankenson KD. Integration of BMP, Wnt, and Notch signaling pathways in osteoblast differentiation. *J Cell Biochem*. 2011 Jul 25. [Epub ahead of print] [Abstract]

Nicolaije C, Koedam M, van Leeuwen JP. Decreased oxygen tension lowers reactive oxygen species and apoptosis and inhibits osteoblast matrix mineralization through changes in early osteoblast differentiation. *J Cell Physiol*. 2011 May 20. [Epub ahead of print] [Abstract]

Okamoto M, Murai J, Imai Y, Ikegami D, Kamiya N, Kato S, Mishina Y, Yoshikawa H, Tsumaki N. Conditional deletion of Bmpr1a in differentiated osteoclasts increases osteoblastic bone formation, increasing volume of remodeling bone in mice. *J Bone Miner Res*. 2011 Jul 22. [Epub ahead of print] [Abstract]

Sul OJ, Ke K, Kim WK, Kim SH, Lee SC, Kim HJ, Kim SY, Suh JH, Choi HS. Absence of MCP-1 leads to elevated bone mass via impaired actin ring formation. *J Cell Physiol*. 2011 Jun 15.

[Epub ahead of print] [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 Jul;96(7):2216-26. [Abstract]

Wu H, Teng PN, Jayaraman T, Onishi S, Li J, Bannon L, Huang H, Close J, Sfeir C. Dentin matrix protein 1 (DMP1) signals via cell surface integrin. *J Biol Chem*. 2011 Jun 3. [Epub ahead of print] [Abstract]

Yang S, Xu H, Yu S, Cao H, Fan J, Ge C, Fransceschi RT, Dong HH, Xiao G. Foxo1 mediates insulin-like growth factor 1 (IGF1)/insulin regulation of osteocalcin expression by antagonizing Runx2 in osteoblasts. *J Biol Chem*. 2011 May 27;286(21):19149-58. [Abstract] [Full Text]

Zhao J, Bradfield JP, Li M, Zhang H, Mentch FD, Wang K, Sleiman PM, Kim CE, Glessner JT, Frackelton EC, Chiavacci RM, Berkowitz RI, Zemel BS, Hakonarson H, Grant SF. BMD-associated variation at the osterix locus is correlated with childhood obesity in females. *Obesity (Silver Spring)*. 2011 Jun;19(6):1311-4. [Abstract]

Zhu W, Liang G, Huang Z, Doty SB, Boskey AL. Conditional inactivation of the CXCR4 receptor in osteoprecursors reduces postnatal bone formation due to impaired osteoblast development. *J Biol Chem*. 2011 Jul 29;286(30):26794-805. [Abstract] [Full Text]

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.