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NOT TO BE MISSED

Clinical and Basic Research Papers – July 2008

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Bone Modeling, Remodeling and Repair

Augat P, Claes L. Increased cortical remodeling after osteotomy causes posttraumatic osteopenia. *Bone*. 2008 Jun 27; [Epub ahead of print] [Abstract]

> *This very nice sheep study showed rapid loss of bone mineral (16%) in the osteotomized limb after fixation. This correlated highly with increases in osteonal cortical remodeling. Load shielding by the osteosynthesis material and local recruitment of bone mineral are likely causes for this increased remodeling. The authors suggest that this bone loss could be moderated by anti-resorptive medication, and complications like refracture or failure of implant fixation could potentially be reduced.* —DGL

de Amorim FP, Ornelas SS, Diniz SF, Batista AC, da Silva TA. Imbalance of RANK, RANKL and OPG expression during tibial fracture repair in diabetic rats. *J Mol Histol*. 2008 Jul 1; [Epub ahead of print] [Abstract]

> *Fracture healing is often delayed in diabetes. Decreased peripheral perfusion and aberrant metabolism may account for these changes. In this study, fracture healing was examined in alloxan-induced diabetic rats, with a focus on RANK/RANKL/OPG expression by RT-PCR and IHC. Expression of all of these was lower in diabetic rats, but the RANKL/OPG ratio was significantly higher in the diabetic group.* —DGL

Lee DY, Yeh CR, Chang SF, Lee PL, Chien S, Cheng CK, Chiu JJ. Integrin-mediated expression of bone formation-related genes in osteoblast-like cells in response to fluid shear stress: roles of extracellular matrix, Shc, and mitogen-activated protein kinase. *J Bone Miner Res*. 2008 Jul;23(7):1140-9. [Abstract]

> *Integrins play significant roles in mechanical responses of cells on extracellular matrix (ECM). This paper provides insight into the underlying mechanisms by studying the roles of integrins and several ECM proteins in shear-mediated signaling and the expression of bone formation-related genes in human osteosarcoma MG63 cells. The findings show that β1 integrin plays predominant roles in shear-induced signaling and gene expression in osteoblast-like MG63 cells on fibronectin, type I collagen, and laminin, and that αvβ3 also plays significant roles in such responses in cells on fibronectin.* —HWD

Manigrasso MB, O'Connor JP. Comparison of fracture healing among different inbred mouse strains. *Calcif Tissue Int*. 2008 Jun 6; [Epub ahead of print] [Abstract]

> *This study examined the effects of mouse strain on outcome in a closed femoral fracture model. The C57BL/6, DBA/2, and C3H inbred strains were considered in terms of radiological, histological, and biomechanical outcomes. C57BL/6 mice showed the*

greatest bone healing response in terms of all outcome measures. C3H>DBA/2 mice displayed a greater initial anabolic response in terms of early callus formation, but by 4 weeks DBA/2>C3H mice exhibited higher biomechanical strength. This study is a pertinent follow up to an early study by Li et al. (Genetic variation in bone-regenerative capacity among inbred strains of mice. Bone. 2001 Aug;29(2):134-40) that looked at the bone and soft tissue regenerative capacity of 12 strains, including the C57BL/6, DBA/1J, and C3H lines. Li et al. found no correlation between bone healing in their vertebral drill-hole model and tissue repair in their ear punch model. Moreover, the C57BL/6 strain was amongst the worst strains for bone regeneration, but amongst the best for tissue regeneration. Thus the recent paper by Manigrasso and O'Connor may indicate that fracture healing represents a combination of general tissue repair and specialized bone formation that is poorly represented by more simplistic models. —DGL

Ono N, Nakashima K, Rittling SR, Schipani E, Hayata T, Soma K, Denhardt DT, Kronenberg HM, Ezura Y, Noda M. Osteopontin negatively regulates parathyroid hormone receptor signaling in osteoblasts. *J Biol Chem*. 2008 Jul 11;283(28):19400-9.

Osteopontin is another main non-collagenous protein of the bone extracellular matrix, which on one side plays a somewhat opposite role to bone sialoprotein (BSP) on bone mineralization, while on another side has also been implicated in OVX-induced bone remodeling. These authors had previously reported that intermittent PTH effects on bone were increased in OPN-deficient mice. Now they report a cross of OPN KO mice with "PPR" mice expressing the constitutively active PTH1R (H223R) from Jansen's metaphyseal dysplasia. They observed that in the absence of OPN, the high cancellous bone phenotype of PPR mice was magnified, in fact resembling an osteopetrotic phenotype. The number of osteoblastic cells on bone surfaces was enhanced, leading the authors to conclude that these results suggest that PTH signaling and transcriptional activity in bone-forming cells is under negative control of the bone matrix protein, osteopontin. —SF

Valverde P, Zhang J, Fix A, Zhu J, Ma W, Tu Q, Chen J. Overexpression of bone sialoprotein leads to an uncoupling of bone formation and bone resorption in mice. *J Bone Miner Res*. 2008 Jul 2; [Epub ahead of print] [Abstract]

Bone sialoprotein (BSP) is a major non-collagenous protein of the bone extracellular matrix. Early studies indicated that it was involved in the initiation of bone mineralization and co-activation of osteoclasts. This study presents a mouse model in which overexpression of BSP led to shorter body and femur length, lower bone mass and trabecular bone volume. These features were associated with increased osteoclastogenesis and bone resorption, supporting a role for BSP in bone remodeling, in addition to mineralization. —SF

Zhao H, Ito Y, Chappel J, Andrews NW, Teitelbaum SL, Ross FP. Synaptotagmin VII regulates bone remodeling by modulating osteoclast and osteoblast secretion. *Dev Cell*. 2008 Jun;14(6):914-25. [Abstract]

Bone resorption by osteoclasts and matrix protein secretion by osteoblasts both require the fusion of secretory vesicles. Synaptotagmin (Syt) family proteins are required for the specific spatio-temporal control of secretory vesicle fusion with the plasma membrane. Among the 15 family members of Syt proteins, Syt VII is expressed broadly, including in macrophages and fibroblasts, and regulates calcium-dependent exocytosis. Thus, the authors tested whether Syt VII regulates secretory processes in osteoblasts and osteoclasts by creating Syt VII(-/-) mice. Syt VII(-/-) mice showed osteopenia with reduced cathepsin K secretion and ruffled border formation in osteoclasts and decreased

matrix protein deposition without change in the differentiation of these cells. It is of interest that a single protein that regulates secretory activities can influence both processes of bone remodeling and affect bone mass. —TM

Cancer and Bone

Miller RE, Roudier M, Jones J, Armstrong A, Canon J, Dougall WC. RANK ligand inhibition plus docetaxel improves survival and reduces tumor burden in a murine model of prostate cancer bone metastasis. *Mol Cancer Ther*. 2008 Jul 7; [Epub ahead of print] [Abstract]

In a murine model of prostate cancer by intracardiac injection, OPG-Fc is shown not only to prevent osteoclastogenesis and bone erosions, but in combination with docetaxel to prevent metastasis by promoting cell death mechanisms (apoptosis) and thereby improving survival. These findings further support the development of human trials on denosumab in prostate cancer. —SF

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 Jul 1;112(1):196-207. [Abstract]

We already knew that Dickkopf1 (Dkk1) production by myeloma cells plays a major role in the absence of osteoblastic response to osteolysis. This paper now demonstrates that Dkk1 is also responsible for the myeloma-induced suppression of osteoblast OPG production, thereby providing further evidence that targeting Dkk1 in multiple myeloma may prevent osteolytic lesions from developing. —SF

Clinical Studies and Drug Effects

Arlot M, Burt-Pichat B, Roux J, Vashishth D, Bouxsein M, Delmas P. Microarchitecture influences microdamage accumulation in human vertebral trabecular bone. *J Bone Miner Res*. 2008 Jun 2; [Epub ahead of print] [Abstract]

Microcrack density (Cr.Dn) in cancellous bone from human lumbar (L2) vertebral bodies from 23 donors aged 54-93 years increased with age and correlated with BV/TV, trabecular number (Tb.N), structure model index (SMI) and trabecular separation (Tb.Sp). Women had higher Cr.Dn than men. SMI explained 35% of the variance in Cr.Dn and 20% of the variance in diffuse damage accumulation. Microcrack length was greater in the highest versus lowest tertiles of SMI. Microdamage is associated with low BV/TV and rod-like trabeculae. —ES

Cauley JA, Ensrud KE. Considering competing risks . . . Not all black and white. *Arch Intern Med*. 2008 Apr 28;168(8):793-5. [Info]

In this brilliant editorial, the authors compare the evidence for an association between glitazones and increased fracture risk, and between bisphosphonate use and risk of atrial fibrillation. Using pre-defined criteria to establish causality, they conclude to firm evidence of the former, but inconsistent evidence for the latter. —SF

Curtis JR, Westfall AO, Cheng H, Delzell E, Saag KG. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. *Osteoporos Int*. 2008 May 16; [Epub ahead of print] [Abstract]

The authors examined the rate of hip fracture among 9063 women who discontinued bisphosphonates versus those who remained on therapy at 2 years. Hip fracture incidence among women who discontinued versus those who did not was 8.43 versus 4.67 per 1000 person years (p = 0.016). —ES

Griffith JF, Yeung DK, Tsang PH, Choi KC, Kwok TC, Ahuja AT, Leung KS, Leung PC. Compromised bone marrow perfusion in osteoporosis. *J Bone Miner Res*. 2008 Jul;23(7):1068-75. [Abstract]

This study used MR techniques to evaluate perfusion and fat content of the proximal femur in normal, osteopenic and osteoporotic subjects. DXA-derived BMD and age were also analyzed. The repeatability for the MR method was shown to be good to excellent by ICC. According to the resulting model, (1) BMD and age, (2) BMD and fat content, and (3) perfusion and fat content are all inversely related. For normal BMD subjects, perfusion in the femoral head was around 1/3 of that in the femoral neck or shaft and 1/5 of that above the acetabulum. Perfusion throughout the proximal femur is reduced in osteoporotic subjects compared with osteopenic and normal subjects. Importantly, this reduction in perfusion only affects bone and not those tissues outside of bone with the same blood supply. This implicates a bone-specific or perhaps even bone-induced regulation of local perfusion. This study does not explain the mechanism but establishes this much neglected field as an area for further mechanistic study. —DGL

Iwamoto J, Matsumoto H, Takeda T, Sato Y, Liu X, Yeh JK. Effects of vitamin K(2) and risedronate on bone formation and resorption, osteocyte lacunar system, and porosity in the cortical bone of glucocorticoid-treated rats. *Calcif Tissue Int*. 2008 Jun 10; [Epub ahead of print] [Abstract]

I recommend this paper because the authors go beyond BMD and look at morphology. Glucocorticoids decreased cortical area and increased marrow area due to decreased periosteal bone formation, increased endocortical erosion, and increased cortical porosity. Vitamin K(2) prevented the reduction in periosteal bone formation. Risedronate prevented a reduction in periosteal bone formation and endocortical erosion. Both increased osteocyte density and lacunar occupancy and prevented a glucocorticoid-induced increase in cortical porosity. —ES

Mellström D, Vandenput L, Mallmin H, Holmberg AH, Lorentzon M, Odén A, Johansson H, Orwoll ES, Labrie F, Karlsson MK, Ljunggren O, Ohlsson C. Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J Bone Miner Res*. 2008 Jun 2; [Epub ahead of print] [Abstract]

Estrogen is my favorite hormone. In 2639 men, fracture incidence during 3.3 years was 2/100 person-years. While associations with sex steroids were reported, free estradiol (E2) and sex hormone-binding globulin (SHBG), not free testosterone (T), were independently associated with fracture risk. Free E2 was inversely associated with clinical vertebral fractures, non-vertebral osteoporosis fractures and hip fractures. —ES

Parker MJ, White A, Boyle A. Fixation versus hemiarthroplasty for undisplaced intracapsular hip fractures. *Injury*. 2008 Jul;39(7):791-5. [Abstract]

This retrospective study looked at outcomes from a prospectively collected database after undisplaced intracapsular hip fractures treated by either internal fixation or hemiarthroplasty. At 1 year from injury all surviving patients were either assessed in a hip fracture clinic or completed a phone call follow-up assessment. 346 matched pairs were analyzed. Patients treated by internal fixation had a shorter operation time (43 versus 67

min), reduced orthopedic ward stay (11 versus 15 days), lower incidence of peri-operative complications (24 versus 81), and a lower 1-year mortality (19% versus 26%). At 1 year, 196 surviving matched pairs were available for comparison, and internal fixation patients had less pain, a lesser reduction in mobility and lower dependence on walking aids. There was a higher reoperation rate with internal fixation, but this did not affect the final outcome. This study strongly suggests that undisplaced fractures are better treated with internal fixation, but it is not a randomized trial, so further study is required. In displaced fractures, there is broad agreement that arthroplasty is superior in the elderly. —DGL

Shimizu H, Nakagami H, Osako MK, Hanayama R, Kunugiza Y, Kizawa T, Tomita T, Yoshikawa H, Ogihara T, Morishita R. Angiotensin II accelerates osteoporosis by activating osteoclasts. *FASEB J*. 2008 Jul;22(7):2465-75. [Abstract]

After thiazides, statins, and β-blockers, it is now the turn of another class of CV drugs, namely ACE inhibitors and Angiotensin II (AngII) receptor antagonists, to gain popularity for their potential role in reducing fracture risk. This work provides experimental evidence that AngII promotes RANKL expression in osteoblasts. In turn, olmesartan, an AngII receptor inhibitor used as an anti-hypertensive agent, prevented these effects. In vivo, AngII increased bone resorption and bone loss in OVX rodents while olmesartan partially prevented it in OVX hypertensive (but not normotensive) rats. —SF

Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab*. 2008 Jun 3; [Epub ahead of print]

This small paper reports 3 subjects with brittle chalkstick fractures of the femur after long-term bisphosphonate therapy. While not the largest study to date of these fractures, previously reported by the groups of Odvina, Goh and Lane, the report reinforces the presence of these fractures in multiple geographic locations. The fracture location, type, bilaterality, prodromal pain and delayed healing were atypical for uncomplicated postmenopausal osteoporosis. All three subjects had concomitant circumstances (endogenous estrogen) or medications (glucocorticoids, hormone replacement therapy, raloxifene) that likely suppressed bone remodeling beyond the effect of the bisphosphonate alone. The patients had suppressed turnover and two were biopsied with confirmation of suppression. Difficulties in healing were seen as previously reported. The group speculates that these patients had severely suppressed turnover because of additional medications and an underlying susceptibility that are to blame for the problems in this subset. —DGL

Whyte MP, McAlister WH, Novack DV, Clements KL, Schoenecker PL, Wenkert D. Bisphosphonate-induced osteopetrosis: novel bone modeling defects, metaphyseal osteopenia, and osteosclerosis fractures after drug exposure ceases. *J Bone Miner Res*. 2008 May 27; [Epub ahead of print] [Abstract]

The authors previously reported (N Eng J Med. 2003 Jul 31;349(5):457-63) a 12-year-old boy who developed osteopetrosis (OPT) while receiving pamidronate (PMD). At 17 years, he had less bone pain, but further limb fractures. His growth plates were fused, hyperphosphatasemia persisted. He had fractures of a metacarpal, an osteosclerotic distal radius, and a dense diaphyseal segment of an ulna where the "chalkstick" break remained incompletely healed after 2 years. There was new L(4) spondylolysis, and previous L(5) spondylolysis had caused spondylolisthesis. Modeling disturbances of OPT persisted. Metaphyseal osteosclerosis had remodeled imperfectly. Newer metaphyseal bone was osteopenic. Femoral necks had become short and wide with an abnormal contour. A "bone-within-bone" configuration was present. In vertebrae, endplates were

thin and trabecular osteopenia was present. Bone mineral density was normal. Bisphosphonate toxicity during childhood can impair skeletal modeling and remodeling. —ES

Yang L, Maric I, McCloskey EV, Eastell R. Shape, structural properties, and cortical stability along the femoral neck: a study using clinical QCT. *J Clin Densitom*. 2008 Jun 10; [Epub ahead of print] [Abstract]

I recommend this study because it demonstrates the complexity of the structure of the femoral neck (FN) and the need for multiple measurements to assess structural properties. Using QCT in 27 postmenopausal women, the authors report increasing ellipticity in cross-sectional shape and tensile and compressive section moduli from the proximal to distal half of the FN. The section modulus was dependent on the fall direction and the cortical thickness varied by site. The notion of a single shape, single cortical thickness of single diameter of a femoral neck belongs to the last century and those believing otherwise should go back there. —ES

Genetics

Guerrini MM, Sobacchi C, Cassani B, Abinun M, Kilic SS, Pangrazio A, Moratto D, Mazzolari E, Clayton-Smith J, Orchard P, Coxon FP, Helfrich MH, Crockett JC, Mellis D, Vellodi A, Tezcan I, Notarangelo LD, Rogers MJ, Vezzoni P, Villa A, Frattini A. Human osteoclast-poor osteopetrosis with hypogammaglobulinemia due to TNFRSF11A (RANK) mutations. *Am J Hum Genet*. 2008 Jul;83(1):64-76. [Abstract]

These authors previously reported RANKL gene (TNFSF11) mutations that were responsible for a subgroup of autosomal recessive osteopetrosis. Now they report additional patients with osteoclast-poor osteopetrosis due to RANK gene mutations. Interestingly, the younger cases also presented with a B cell subset deficiency and low immunoglobulin levels, a feature which was absent in RANKL-deficient subjects. In contrast, T cell and dendritic cell number and functions were intact. These findings newly raise the question of the role of RANK-mediated signaling, as opposed to RANKL binding and activation, on immune functions. This topic will be broadly reviewed in a BoneKEy Perspective this fall. —SF

Zhang H, Sol-Church K, Rydbeck H, Stabley D, Spotila LD, Devoto M. High resolution linkage and linkage disequilibrium analyses of chromosome 1p36 SNPs identify new positional candidate genes for low bone mineral density. *Osteoporos Int*. 2008 Jul 3; [Epub ahead of print] [Abstract]

The chromosomal region 1p36 has been identified in linkage and association to BMD and other osteoporosis phenotypes in a number of studies, including the recent GWAS (see Xiong et al. IBMS BoneKEy. 2008 May;5(5):182-5), however, the gene(s) therein implicated in the control of bone mass remain largely unknown. Pursuing their seminal work on mapping the osteoporosis genes on 1p36, these authors have used high-density SNPs at this locus to identify a number of potential candidate genes, including RERE and G1P2. —SF

Molecular and Cell Biology

Bozec A, Bakiri L, Hoebertz A, Eferl R, Schilling AF, Komnenovic V, Scheuch H, Priemel M, Stewart CL, Amling M, Wagner EF. Osteoclast size is controlled by Fra-2 through LIF/LIF-receptor signaling and hypoxia. *Nature*. 2008 Jul 10;454(7201):221-5. [Abstract]

Using Fra-2-deficient mice, this study demonstrates that Fra-2 deficiency reduces transcription of LIF, and reduced LIF signaling suppresses the transcription of HIF prolyl hydroxylase PHD2 in the placenta. PHD2 is the key oxygen sensor and regulates the stability of HIF. Placenta-induced hypoxia enhances HIF1α in bone during embryogenesis, leading to Bcl-2 expression that causes an increased number and size of osteoclasts. In mice deficient in Fra-2 in tissues other than the placenta, hypoxia is not observed in bone and osteoclasts do not show any phenotypic changes, suggesting that placenta-induced hypoxia is responsible for the development of giant osteoclasts in bone. It will be interesting to see if disorders with an increased number and size of osteoclasts are related to a hypoxic environment in bone. —TM

Guo R, Yamashita M, Zhang Q, Zhou Q, Chen D, Reynolds DG, Awad HA, Yanoso L, Zhao L, Schwarz EM, Zhang YE, Boyce BF, Xing L. Ubiquitin ligase Smurf1 mediates TNF-induced systemic bone loss by promoting proteasomal degradation of BMP signaling proteins. *J Biol Chem*. 2008 Jun 19; [Epub ahead of print]

A new mechanism underlying TNF-α negative effects on the bone mineral balance is reported here. Namely, altered bone microarchitecture and strength of TNF transgenic mice was partially rescued in a cross with Smurf1 KO mice that prevented TNF-induced activation of the proteasome-ubiquitin system and degradation of Smad 1 and Runx2. —SF

Kuroda Y, Hisatsune C, Nakamura T, Matsuo K, Mikoshiba K. Osteoblasts induce Ca2+ oscillation-independent NFATc1 activation during osteoclastogenesis. *Proc Natl Acad Sci U S A*. 2008 Jun 24;105(25):8643-8. [Abstract] [Full Text]

Everybody knows that RANKL and M-CSF are indispensable factors for osteoclastogenesis. Yet, is RANKL a crucial mediator of osteoblast-induced osteoclastogenesis? By investigating bone marrow cells from mice deficient in inositol trisphosphate receptor (IP3-R2), it is shown here that osteoblasts may promote osteoclastogenesis through NFATc1 activation but independently of RANKL/M-CSF and calcium oscillations. Now, what is the new osteoblastic factor involved here? —SF

McLachlan E, Plante I, Shao Q, Tong D, Kidder GM, Bernier SM, Laird DW. ODDD-linked Cx43 mutants reduce endogenous Cx43 expression and function in osteoblasts and inhibit late stage differentiation. *J Bone Miner Res*. 2008 Jun;23(6):928-38. [Abstract]

Bone development and modeling require precise gap junctional intercellular communication (GJIC). Mutations of the GJA1 gene, encoding the gap junction protein, connexin43 (Cx43), can cause oculodentodigital dysplasia (ODDD). In this paper, the authors hypothesize and then demonstrate that Cx43 mutation causes osteoblast dysfunction, which may contribute to the bone phenotype of ODDD. The results show that expression of human and mouse ODDD-linked Cx43 mutants failed to significantly impair differentiation in cells predisposed to the osteoblast lineage; however, germ line reduction of Cx43-based GJIC leads to impaired osteoblast differentiation, which may account for the bone phenotypes observed in ODDD patients. —HWD

Yamaza T, Miura Y, Bi Y, Liu Y, Akiyama K, Sonoyama W, Patel V, Gutkind S, Young M, Gronthos S, Le A, Wang CY, Chen W, Shi S. Pharmacologic stem cell based intervention as a new approach to osteoporosis treatment in rodents. *PLoS ONE*. 2008 Jul 9;3(7):e2615. [Abstract]

Did you ever think of aspirin for restoring the bone mineral balance after estrogen-deprivation? This study presents an impressive number of in vitro and in vivo

experiments demonstrating that activated T cells are implicated in the apoptosis of mesenchymal stem cells (MSCs) and inhibition of osteogenic differentiation, in addition to supporting osteoclastogenesis. Moreover, aspirin induced T cell death, thereby preventing MSC apoptosis and restoring bone mineralization in vitro and in OVX mice, with an improvement of microstructural alterations. These very intriguing results will be further discussed in a BoneKEy Commentary this fall. —SF

Reviews, Perspectives and Editorials

Ackerman KE. Is denosumab a safe and effective treatment for postmenopausal osteoporosis? *Nat Clin Pract Endocrinol Metab*. 2008 Jul;4(7):376-7. [Info]

Compston J, Reid DM, Boisdron J, Brandi ML, Burlet N, Cahall D, Delmas PD, Dere W, Devogelaer JP, Fitzpatrick LA, Flamion B, Goel N, Korte S, Laslop A, Mitlak B, Ormarsdottir S, Ringe J, Rizzoli R, Tsouderos Y, Van Staa T, Reginster JY. Recommendations for the registration of agents for prevention and treatment of glucocorticoid-induced osteoporosis: an update from the Group for the Respect of Ethics and Excellence in Science. *Osteoporos Int*. 2008 Jul 5; [Epub ahead of print] [Info]

Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: a growing concern. *Kidney Int*. 2008 Jun 18; [Epub ahead of print] [Abstract]

Silkstone D, Hong H, Alman BA. beta-Catenin in the race to fracture repair: in it to Wnt. *Nat Clin Pract Rheumatol*. 2008 Jun 17; [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Addison W, Nakano Y, Loisel T, Crine P, McKee M. MEPE-ASARM peptides control extracellular matrix mineralization by binding to hydroxyapatite - an inhibition regulated by PHEX cleavage of ASARM. *J Bone Miner Res*. 2008 Jul 2; [Epub ahead of print] [Abstract]

Aqeilan RI, Hassan MQ, de Bruin A, Hagan JP, Volinia S, Palumbo T, Hussain S, Lee SH, Gaur T, Stein GS, Lian JB, Croce CM. The WWOX tumor suppressor is essential for post-natal survival and normal bone metabolism. *J Biol Chem*. 2008 May 16; [Epub ahead of print]

Baldridge D, Schwarze U, Morello R, Lennington J, Bertin TK, Pace JM, Pepin MG, Weis M, Eyre DR, Walsh J, Lambert D, Green A, Robinson H, Michelson M, Houge G, Lindman C, Martin J, Ward J, Lemyre E, Mitchell JJ, Krakow D, Rimoin DL, Cohn DH, Byers PH, Lee B. CRTAP and LEPRE1 mutations in recessive osteogenesis imperfecta. *Hum Mutat*. 2008 Jun 19; [Epub ahead of print] [Abstract]

Beck TJ, Michael Lewiecki E, Miller PD, Felsenberg D, Liu Y, Ding B, Libanati C. Effects of denosumab on the geometry of the proximal femur in postmenopausal women in comparison with alendronate. *J Clin Densitom*. 2008 May 19; [Epub ahead of print] [Abstract]

Berger C, Langsetmo L, Joseph L, Hanley DA, Davison KS, Josse R, Kreiger N, Tenenhouse A, Goltzman D; Canadian Multicentre Osteoporosis Study Research Group. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. *CMAJ*. 2008 Jun 17;178(13):1660-8. [Abstract]

Buxton PG, Bitar M, Gellynck K, Parkar M, Brown RA, Young AM, Knowles JC, Nazhat SN. Dense collagen matrix accelerates osteogenic differentiation and rescues the apoptotic response to MMP inhibition. *Bone*. 2008 Aug;43(2):377-85. [Abstract]

Chandhoke TK, Huang YF, Liu F, Gronowicz GA, Adams DJ, Harrison JR, Kream BE. Osteopenia in transgenic mice with osteoblast-targeted expression of the inducible cAMP early repressor. *Bone*. 2008 Jul;43(1):101-9. [Abstract]

de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW. Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. *Osteoporos Int*. 2008 Jul;19(7):1029-37. [Abstract]

Duplomb L, Baud'huin M, Charrier C, Berreur M, Trichet V, Blanchard F, Heymann D. Interleukin-6 inhibits receptor activator of nuclear factor kappaB ligand-induced osteoclastogenesis by diverting cells into the macrophage lineage: key role of Serine727 phosphorylation of signal transducer and activator of transcription 3. *Endocrinology*. 2008 Jul;149(7):3688-97. [Abstract] [Full Text]

Elabd C, Basillais A, Beaupied H, Breuil V, Wagner N, Scheideler M, Zaragosi LE, Massiéra F, Lemichez E, Trajanoski Z, Carle G, Euller-Ziegler L, Ailhaud G, Benhamou CL, Dani C, Amri EZ. Oxytocin controls differentiation of human mesenchymal stem cells and reverses osteoporosis. *Stem Cells*. 2008 Jun 26; [Epub ahead of print] [Abstract]

Giudici C, Raynal N, Wiedemann H, Cabral WA, Marini JC, Timpl R, Bächinger HP, Farndale RW, Sasaki T, Tenni R. Mapping of SPARC/BM-40/osteonectin-binding sites on fibrillar collagens. *J Biol Chem*. 2008 Jul 11;283(28):19551-60. [Abstract] [Full Text]

Hawse JR, Subramaniam M, Monroe DG, Hemmingsen AH, Ingle JN, Khosla S, Oursler MJ, Spelsberg TC. Estrogen receptor beta isoform-specific induction of transforming growth factor beta-inducible early gene-1 in human osteoblast cells: an essential role for the activation function 1 domain. *Mol Endocrinol*. 2008 Jul;22(7):1579-95. [Abstract] [Full Text]

Hewitt J, Lu X, Gilbert L, Nanes MS. The muscle transcription factor MyoD promotes osteoblast differentiation by stimulation of the Osterix promoter. *Endocrinology*. 2008 Jul;149(7):3698-707. [Abstract] [Full Text]

Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone*. 2008 Aug;43(2):312-21. [Abstract]

Kelchtermans H, Geboes L, Mitera T, Huskens D, Leclercq G, Matthys P. Activated CD4+CD25+ regulatory T cells inhibit osteoclastogenesis and collagen-induced arthritis. *Ann Rheum Dis*. 2008 May 14; [Epub ahead of print]

Langsetmo LA, Morin S, Richards JB, Davison KS, Olszynski WP, Prior JC, Josse R, Goltzman D; CaMos Research Group. Effectiveness of antiresorptives for the prevention of nonvertebral low-trauma fractures in a population-based cohort of women. *Osteoporos Int*. 2008 Jun 26; [Epub ahead of print] [Abstract]

Li X, Huang M, Zheng H, Wang Y, Ren F, Shang Y, Zhai Y, Irwin DM, Shi Y, Chen D, Chang Z. CHIP promotes Runx2 degradation and negatively regulates osteoblast differentiation. *J Cell Biol*. 2008 Jun 16;181(6):959-72. [Abstract] [Full Text]

Li X, Pennisi A, Yaccoby S. Role of decorin in the antimyeloma effects of osteoblasts. *Blood*. 2008 Jul 1;112(1):159-68. [Abstract]

Machado do Reis L, Kessler CB, Adams DJ, Lorenzo J, Jorgetti V, Delany AM. Accentuated osteoclastic response to parathyroid hormone undermines bone mass acquisition in osteonectin-null mice. *Bone*. 2008 Aug;43(2):264-73. [Abstract]

Mahoney DJ, Mikecz K, Ali T, Mabilleau G, Benayahu D, Plaas A, Milner CM, Day AJ, Sabokbar A. TSG-6 regulates bone remodelling through inhibition of osteoblastogenesis and osteoclast activation. *J Biol Chem*. 2008 Jun 26; [Epub ahead of print]

Mannstadt M, Bertrand G, Muresan M, Weryha G, Leheup B, Pulusani SR, Grandchamp B, Jüppner H, Silve C. Dominant-negative GCMB mutations cause an autosomal dominant form of hypoparathyroidism. *J Clin Endocrinol Metab*. 2008 Jun 26; [Epub ahead of print]

Mastrandrea LD, Wactawski-Wende J, Donahue RP, Hovey KM, Clark A, Quattrin T. Young women with type 1 diabetes have lower bone mineral density that persists over time. *Diabetes Care*. 2008 Jun 30; [Epub ahead of print] [Abstract]

Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. *Arch Intern Med*. 2008 Apr 28;168(8):820-5. [Abstract]

Mörmann M, Thederan M, Nackchbandi I, Giese T, Wagner C, Hänsch GM. Lipopolysaccharides (LPS) induce the differentiation of human monocytes to osteoclasts in a tumour necrosis factor (TNF) alpha-dependent manner: A link between infection and pathological bone resorption. *Mol Immunol*. 2008 Jul;45(12):3330-7. [Abstract]

Mullin BH, Prince RL, Dick IM, Islam FM, Hart DJ, Spector TD, Devine A, Dudbridge F, Wilson SG. Bone structural effects of variation in the TNFRSF1B gene encoding the tumor necrosis factor receptor 2. *Osteoporos Int*. 2008 Jul;19(7):961-8. [Abstract]

Otero JE, Dai S, Foglia D, Alhawagri M, Vacher J, Pasparakis M, Abu-Amer Y. Defective osteoclastogenesis by IKKbeta-null precursors is a result of RANKL-induced JNK-dependent apoptosis and impaired differentiation. *J Biol Chem*. 2008 Jun 19; [Epub ahead of print]

Pan Q, Yu Y, Chen Q, Li C, Wu H, Wan Y, Ma J, Sun F. Sox9, a key transcription factor of bone morphogenetic protein-2-induced chondrogenesis, is activated through BMP pathway and a CCAAT box in the proximal promoter. *J Cell Physiol*. 2008 May 27; [Epub ahead of print] [Abstract]

Panupinthu N, Rogers JT, Zhao L, Solano-Flores LP, Possmayer F, Sims SM, Dixon SJ. P2X7 receptors on osteoblasts couple to production of lysophosphatidic acid: a signaling axis promoting osteogenesis. *J Cell Biol*. 2008 Jun 2;181(5):859-71. [Abstract] [Full Text]

Rajachar RM, Truong AQ, Giachelli CM. The influence of surface mineral and osteopontin on the formation and function of murine bone marrow-derived osteoclasts. *J Mater Sci Mater Med*. 2008 May 16; [Epub ahead of print] [Abstract]

Semenov MV, Zhang X, He X. DKK1 antagonizes Wnt signaling without promotion of LRP6 internalization and degradation. *J Biol Chem*. 2008 May 27; [Epub ahead of print]

Shimada M, Greer PA, McMahon AP, Bouxsein ML, Schipani E. In vivo targeted deletion of calpain small subunit, Capn4, in cells of the osteoblast lineage impairs cell proliferation, differentiation, and bone formation. *J Biol Chem*. 2008 Jul 25;283(30):21002-10. [Abstract] [Full Text]

Shinohara ML, Kim HJ, Kim JH, Garcia VA, Cantor H. Alternative translation of osteopontin generates intracellular and secreted isoforms that mediate distinct biological activities in dendritic cells. *Proc Natl Acad Sci U S A*. 2008 May 20;105(20):7235-9. [Abstract] [Full Text]

Tran BN, Nguyen ND, Eisman JA, Nguyen TV. Association between LRP5 polymorphism and bone mineral density: a Bayesian meta-analysis. *BMC Med Genet*. 2008 Jun 27;9:55. [Abstract]

Trevant B, Gaur T, Hussain S, Symons J, Komm BS, Bodine PV, Stein GS, Lian JB. Expression of secreted frizzled related protein 1, a Wnt antagonist, in brain, kidney, and skeleton is dispensable for normal embryonic development. *J Cell Physiol*. 2008 May 22; [Epub ahead of print] [Abstract]

Tuna H, Birtane M, Ekuklu G, Cermik F, Tuna F, Kokino S. Does quantitative tibial ultrasound predict low bone mineral density defined by dual energy x-ray absorptiometry? *Yonsei Med J*. 2008 Jun 30;49(3):436-42. [Abstract]

Uppal S, Diggle CP, Carr IM, Fishwick CW, Ahmed M, Ibrahim GH, Helliwell PS, Latos-Bieleńska A, Phillips SE, Markham AF, Bennett CP, Bonthron DT. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. *Nat Genet*. 2008 Jun;40(6):789-93. [Abstract]

Upton ML, Gilchrist CL, Guilak F, Setton LA. Transfer of macro-scale tissue strain to micro-scale cell regions in the deformed meniscus. *Biophys J*. 2008 May 16; [Epub ahead of print] [Abstract]

Wu M, Li J, Engleka KA, Zhou B, Lu MM, Plotkin JB, Epstein JA. Persistent expression of Pax3 in the neural crest causes cleft palate and defective osteogenesis in mice. *J Clin Invest*. 2008 Jun;118(6):2076-87. [Abstract]

Yajima A, Inaba M, Tominaga Y, Ito A. Bone formation by minimodeling is more active than remodeling after parathyroidectomy. *Kidney Int*. 2008 Jun 4; [Epub ahead of print] [Abstract]

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