

NOT TO BE MISSED

Clinical and Basic Research Papers – April 2007 Selections

Serge Ferrari, Associate Editor

Ego Seeman, Clinical Editor

Gordon J. Strewler, Editor

Bone Modeling and Remodeling

◆ Zhang Q, Major MB, Takanashi S, Camp ND, Nishiya N, Peters EC, Ginsberg MH, Schultz PG, Moon RT, Ding S. Small-molecule synergist of the Wnt/beta-catenin signaling pathway. *Proc Natl Acad Sci U S A*. 2007 May 1;104(18):7444-8. [[Abstract](#)] [[Full Text](#)]

*Screening a library of small-molecules, the authors identified a compound able to synergize with Wnt 3a to activate the β -catenin signaling pathway. Although its effects on bone are not shown here, there is evidence in *Xenopus* and in vitro that this compound, through an effect on protein trafficking, has dose-dependent biological activity. Its interest as a bone anabolic agent is obvious. —SF*

Genetics

◆ Beamer WG, Shultz KL, Ackert-Bicknell CL, Horton LG, Delahunty KM, Coombs HF, Donahue LR, Canalis E, Rosen CJ. Genetic dissection of mouse distal chromosome 1 reveals three linked BMD QTL with sex dependent regulation of bone phenotypes. *J Bone Miner Res*. 2007 Apr 23; [Epub ahead of print] [[Abstract](#)]

By transferring a region of mouse chromosome 1 from one mouse strain to another, the authors were able to increase various microarchitectural parameters in the recipient (congenic) mouse. Most interestingly, some traits were specifically influenced in males vs. females, arguing for the need to map bone genes specifically by sex. These results should also greatly facilitate the identification of human genes governing bone microstructure, due to the large homology between mouse and human chromosome 1. —SF

◆ Jiao Y, Yan J, Jiao F, Yang H, Donahue LR, Li X, Roe BA, Stuart J, Gu W. A single nucleotide mutation in *Nppc* is associated with a long bone abnormality in *lbab* mice. *BMC Genet*. 2007 Apr 17;8:16. [[Abstract](#)]

*In the long bone abnormality mouse (*lbab*), which is dwarfed, the authors identified a new single gene mutation in *Nppc*, a gene implicated in natriuretic peptide receptor activity and/or FGF signaling. But the main reason why we bring this paper to attention is because the mutation was mapped although only rough linkage had been performed, thereby demonstrating that with recent high-throughput direct screening methods for mutations, prior fine mapping may not be necessary. Taken together with the fact that the gene is expressed on chromosome 1, one might think that this kind of approach might be useful to quickly solve the genes responsible for differences in bone microarchitecture (see the paper by Beamer et al. above). —SF*

Treatment and Drug Effects

◆Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007 May 3;356(18):1809-22. [[Abstract](#)]

◆Compston J. Treatments for osteoporosis - looking beyond the HORIZON. *N Engl J Med*. 2007 May 3;356(18):1878-80. [[Info](#)]

HORIZON was a randomized, placebo-controlled clinical trial that measured fracture risk over 3 years in 7,765 postmenopausal women who received either a single 15-minute intravenous infusion of zoledronic acid (5 mg) once a year or a placebo. Compared with placebo, treatment with zoledronic acid significantly decreased the risk of vertebral fracture by 70% and the risk of hip fracture by 41%. The drug also significantly lowered the risk of non-vertebral fractures by 25%, the risk of clinical fractures by 33%, and the risk of clinical vertebral fractures by 77%. Bone turnover markers were suppressed at year one with stable levels thereafter. The most significant adverse event was an increased incidence of atrial fibrillation; a letter accompanying the paper reports that a re-analysis of the FIT study of alendronate reveals a trend towards atrial fibrillation that did not reach statistical significance. Once-yearly intravenous zoledronic acid compares favorably to oral bisphosphonates in efficacy and safety. —GJS

◆Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, Blosch CM, Mathisen AL, Morris SA, Marriott TB; Treatment of Osteoporosis with Parathyroid Hormone Study Group. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. *Ann Intern Med*. 2007 Mar 6;146(5):326-39. [[Abstract](#)]

2,532 postmenopausal women with low bone mineral density received 100 µg of recombinant human PTH or placebo daily. Parathyroid hormone reduced the risk for new or worsened vertebral fractures, but the findings were sensitive to assumptions about fracture incidence in patients who did not complete the study. This honest presentation of data provides further evidence of benefits of anabolic agents. More studies are needed. —ES

◆Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007 Apr 4;297(13):1465-77. [[Abstract](#)]

In a secondary analysis of the Women's Health Initiative (WHI) involving 10,739 postmenopausal women who had undergone a hysterectomy and 16,608 who had not, the authors suggest there may be no increased risk in early postmenopausal women, if not a reduced risk despite 95% CI overlapping unity. The issue seems irrelevant given the risk of stroke is increased independent of age or years since menopause (HR, 1.32; 95% CI, 1.12-1.56). —ES

Reviews, Perspectives and Editorials

◆Patel MS, Elefteriou F. The new field of neuroskeletal biology. *Calcif Tissue Int*. 2007 Apr 18; [Epub ahead of print] [[Abstract](#)]

Other Studies of Potential Interest

- ◆ Addison WN, Azari F, Sorensen ES, Kaartinen MT, McKee MD. Pyrophosphate inhibits mineralization of osteoblast cultures by binding to mineral, upregulating osteopontin and inhibiting alkaline phosphatase activity. *J Biol Chem*. 2007 Mar 23; [Epub ahead of print]
- ◆ Betz OB, Betz VM, Nazarian A, Egermann M, Gerstenfeld LC, Einhorn TA, Vrahas MS, Bouxsein ML, Evans CH. Delayed administration of adenoviral BMP-2 vector improves the formation of bone in osseous defects. *Gene Ther*. 2007 Apr 26; [Epub ahead of print] [\[Abstract\]](#)
- ◆ Carter PH, Liu RQ, Foster WR, Tamasi JA, Tebben AJ, Favata M, Staal A, Cvijic ME, French MH, Dell V, Apanovitch D, Lei M, Zhao Q, Cunningham M, Decicco CP, Trzaskos JM, Feyen JH. Discovery of a small molecule antagonist of the parathyroid hormone receptor by using an N-terminal parathyroid hormone peptide probe. *Proc Natl Acad Sci U S A*. 2007 Apr 17;104(16):6846-51. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ Faccio R, Takeshita S, Colaianni G, Chappel J, Zallone A, Teitelbaum SL, Ross FP. M-CSF regulates the cytoskeleton via recruitment of a multimeric signaling complex to c-FMS Y559/697/721. *J Biol Chem*. 2007 Apr 9; [Epub ahead of print]
- ◆ Ford-Hutchinson AF, Ali Z, Lines SE, Hallgrimsson B, Boyd SK, Jirik FR. Inactivation of Pten in osteo-chondroprogenitor cells leads to epiphyseal growth plate abnormalities and skeletal overgrowth. *J Bone Miner Res*. 2007 Apr 24; [Epub ahead of print] [\[Abstract\]](#)
- ◆ Kurata H, Guillot PV, Chan J, Fisk NM. Osterix induces osteogenic gene expression but not differentiation in primary human fetal mesenchymal stem cells. *Tissue Eng*. 2007 Apr 29; [Epub ahead of print] [\[Abstract\]](#)
- ◆ Lu Y, Cai Z, Xiao G, Keller ET, Mizokami A, Yao Z, Roodman GD, Zhang J. Monocyte chemotactic protein-1 mediates prostate cancer-induced bone resorption. *Cancer Res*. 2007 Apr 15;67(8):3646-53. [\[Abstract\]](#)
- ◆ Martin A, David V, Malaval L, Lafage-Proust MH, Vico L, Thomas T. Opposite effects of leptin on bone metabolism: a dose-dependent balance related to energy intake and IGF-I pathway. *Endocrinology*. 2007 Apr 12; [Epub ahead of print]
- ◆ Murshid SA, Kamioka H, Ishihara Y, Ando R, Sugawara Y, Takano-Yamamoto T. Actin and microtubule cytoskeletons of the processes of 3D-cultured MC3T3-E1 cells and osteocytes. *J Bone Miner Metab*. 2007;25(3):151-8. [\[Abstract\]](#)
- ◆ Ueda K, Yamanaka Y, Harada D, Yamagami E, Tanaka H, Seino Y. PTH has the potential to rescue disturbed bone growth in achondroplasia. *Bone*. 2007 Mar 12; [Epub ahead of print] [\[Abstract\]](#)
- ◆ Washio-Oikawa K, Nakamura T, Usui M, Yoneda M, Ezura Y, Ishikawa I, Kazuhisa N, Noda T, Yamamoto T, Noda M. Cnot7 null mice exhibit high bone mass phenotype and modulation of BMP actions. *J Bone Miner Res*. 2007 Apr 23; [Epub ahead of print] [\[Abstract\]](#)

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. 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. Strewler reports that no conflict of interest exists.