

# Endocrinology ROUNDS®

September 2007  
Volume 7, Issue 7

AS PRESENTED IN THE ROUNDS  
OF THE DIVISION OF  
ENDOCRINOLOGY AND METABOLISM,  
ST. MICHAEL'S HOSPITAL

www.endocrinologyrounds.ca

## New Treatment Modalities for Osteoporosis

BY SOPHIE JAMAL, MD, PHD

Over the past decade, there have been many advances in the treatment of osteoporosis and related fractures. For example, Health Canada recently approved the second-generation bisphosphonate, risedronate, for monthly administration, and now, patients with osteoporosis can be offered treatment with the anabolic agent, parathyroid hormone (PTH 1-34). In addition, an increased understanding of the molecular mechanisms in bone remodeling has led to the investigation of several novel and promising treatment modalities for osteoporosis, including denosumab, a monoclonal antibody to receptor activator of nuclear factor- $\kappa$ B ligand (RANKL); strontium ranelate, an agent that both stimulates bone formation and inhibits bone resorption; and sclerostin, an inhibitor of Wnt signaling that may inhibit bone formation.

This issue of *Endocrinology Rounds* reviews the bone remodeling cycle – the target of all osteoporosis treatments. The existing data supporting the use of monthly risedronate, PTH, denosumab, strontium, and sclerostin for osteoporosis prevention and treatment are also reviewed and pragmatic advice on the clinical utility of these agents is provided.

### The bone remodeling cycle

Bone is a complex tissue that is composed of several cell types that are continuously undergoing a process of renewal and repair termed “bone remodeling.” Bone remodeling is critical for repairing microfractures or fatigue damage that occur as a result of daily wear and tear on the skeleton. There are 3 cell types responsible for bone remodeling:

- osteocytes that detect microdamage and control the process of bone remodeling
- osteoclasts that resorb or break down bone
- osteoblasts that form new bone.<sup>1,2</sup>

Osteocytes originate from osteoblasts that remain trapped in the bone after it has been formed and are thought to control the bone-remodeling process. Osteoclasts are multinucleated cells that differentiate from the precursors in the monocyte/macrophage lineage in response to a coordinated expression of specific regulatory molecules, including RANK (receptor activator of NF $\kappa$ B), and its ligand (RANKL). Differentiation of osteoclasts is blocked by osteoprotegerin (OPG) that acts as a decoy receptor for RANKL (Figure 1).<sup>3</sup> Osteoblasts differentiate from bone marrow stromal cells in response to activation of the transcription factor, core binding factor  $\alpha$ 1 (Cbf $\alpha$ 1).<sup>4</sup>

During bone remodeling, osteoclasts remove old or damaged bone by attaching to its surface and forming a skirt (a “ruffled border”) around its circumference. This process creates a pocket that the osteoclasts fill with hydrochloric acid and proteolytic enzymes to dissolve the mineral and protein of the bone beneath it. Subsequently, the osteoclasts migrate away from the area of bone under going resorption and undergo apoptosis. Osteoblasts then lay down the protein skeleton (osteoid). Later, the osteoid becomes



Leading with Innovation  
Serving with Compassion

ST. MICHAEL'S HOSPITAL  
A teaching hospital affiliated with the University of Toronto



### Members of the Division of Endocrinology and Metabolism at St. Michael's Hospital

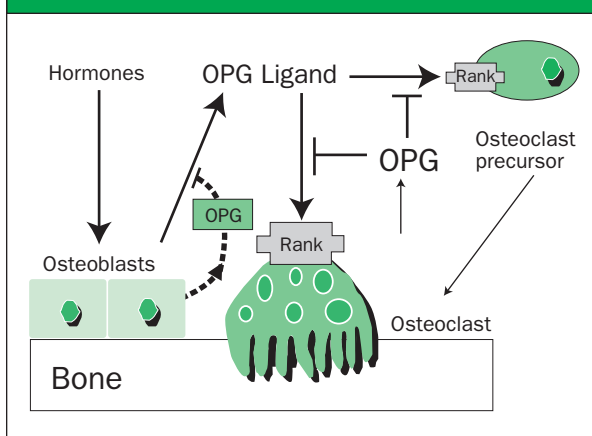
LAWRENCE LEITER, MD (HEAD)  
EDITOR, *ENDOCRINOLOGY ROUNDS*

GILLIAN BOOTH, MD  
ALICE CHENG, MD  
PHILIP CONNELLY, PHD  
CHRISTINE DERZKO, MD  
RICHARD GILBERT, PHD, MD  
JEANNETTE GOGUEN, MD  
LOREN GROSSMAN, MD  
AMIR HANNA, MD  
SOPHIE JAMAL, MD, PHD  
DAVID JENKINS, MD, PHD  
ROBERT JOSSE, MD  
MARIA KRAW, MD  
TIM MURRAY, MD  
DOMINIC NG, PHD, MD  
JOEL RAY, MD  
WILLIAM SINGER, MD  
VLAD VUKSAN, PHD  
QINGHUA WANG, MD, PHD  
TOM WOLEVER, MD, PHD  
MINNA WOO, MD, PHD  
CATHERINE YU, MD

St. Michael's Hospital  
6121-61 Queen St. E.  
Toronto, Ont. M5C 2T2  
Fax: (416) 867-3696

The opinions expressed in this publication do not necessarily represent those of the Division of Endocrinology and Metabolism, St. Michael's Hospital, the University of Toronto, the educational sponsor, or the publisher, but rather are those of the author based on the available scientific literature. The author has been required to disclose any potential conflicts of interest relative to the content of this publication. *Endocrinology Rounds* is made possible by an unrestricted educational grant.

**Figure 1: The RANK, RANKL, OPG axis**



OPG = osteoprotegerin

Adapted from Boyle WJ, et al<sup>14</sup>

mineralized; calcium and hydroxyapatite begin to crystallize around the fibrils of collagen, and the area becomes mature bone.<sup>5</sup> Typically, bone formation and bone resorption are coupled to maintain bone mass, strength, and integrity. However, with increasing age, steroids, and menopause, osteoclast activity (bone resorption) exceeds osteoblast activity (bone formation), and the net result is loss of bone mass and an increased risk of fracture.

### Treatments for osteoporosis

Treatments for osteoporosis can be classified into 2 groups: inhibitors of osteoclast activity or bone resorption (eg, bisphosphonates) and stimulators of osteoblast activity or bone formation (eg, PTH). Table 1 provides a more complete list of the agents currently available for the prevention or treatment of osteoporosis.

Traditionally, inhibitors of bone resorption are referred to as “antiresorptives” and stimulators of bone formation are termed “anabolics.” Recently, a new

**Table 1: Treatments for osteoporosis\***

Inhibitors of bone resorption (anticatabolics)	Stimulators of bone formation (anabolics)
Bisphosphonates*	Fluoride
Systemic estrogen receptor modulators (SERMS)*	Growth factors (growth hormone, IGF 1)
Estrogen*	Strontium ranelate
Calcitonin*	Sclerostin
RANKL inhibitors	Parathyroid hormone (PTH)*

\* Approved by Health Canada for the prevention/treatment of osteoporosis

**Table 2: Practical points: monthly risedronate**

- New dosing regimen of risedronate 75 mg on 2 consecutive days once monthly will soon be available to Canadians.
- Effects on BMD and side effect profile no different than daily risedronate at 12-month follow-up.
- It should be prescribed in the same way as daily risedronate and should be based on patient preference.

nomenclature has been suggested that better reflects the mechanism of action with these agents. Anti-resorptives are now called “anticatabolics” and they act to decrease bone resorption, activation frequency and bone formation, and preserve bone structure and microarchitecture. Anabolics increase bone formation, activation frequency, and bone turnover, inducing microarchitectural changes in bone with the creation of a new bone structure. It should be noted that both classes of drugs reduce fracture risk.

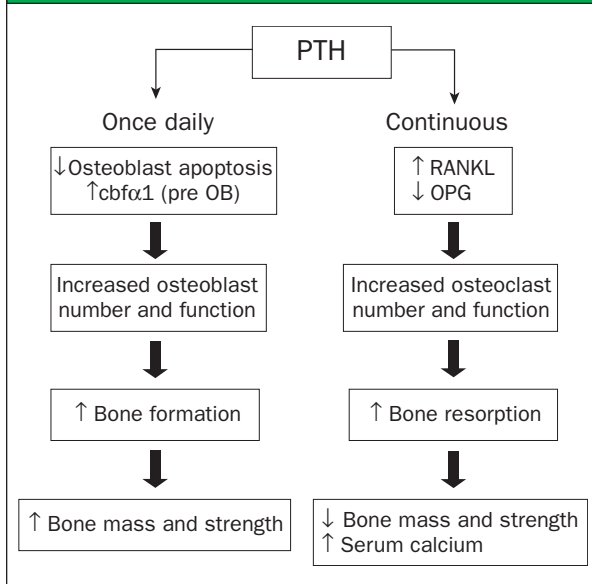
### Risedronate

Risedronate (75 mg), an anticatabolic that is taken on 2 consecutive days each month, has recently been approved by Health Canada. The approval of monthly risedronate was based on a double-blind clinical trial of 1,229 postmenopausal women with osteoporosis aged ≥50 years with a lumbar spine bone mineral density (LS-BMD) T-score greater than -2.5 or an LS-BMD T-score greater than -2.0 and at least 1 prevalent vertebral fracture. In the trial, increases in bone mineral density (BMD) at the lumbar spine, total hip, and hip trochanter in patients treated with monthly risedronate (75 mg, 2 consecutive days) were similar to those in patients treated with risedronate, 5 mg daily, at both time points measured (6 and 12 months). Both treatments were generally well-tolerated and there were similar adverse events in the two groups. The availability of monthly dosing increases the number of treatment options available for Canadians with osteoporosis. Table 2 highlights practical points about risedronate prescribing.

### Parathyroid hormone

At first consideration, using PTH as an anabolic agent seems counterintuitive. Indeed, patients with hyperparathyroidism have elevated levels of PTH, bone loss, and fractures. The reason for the paradoxical effects is due to the dosing regimen. When given

**Figure 2: Frequency of administration of PTH determines effects**



continuously, PTH stimulates RANKL and inhibits OPG (Figure 2), resulting in increased osteoclast activity, increased bone resorption, decreased bone mass and strength, and increased fractures. In contrast, when PTH is administered once daily, as it is for osteoporosis, there is a decrease in osteoblast apoptosis, and increases in Cbfa1, osteoblast number and function, and bone formation, mass, and strength. Figure 2 outlines the differential effects of PTH based on frequency of administration.

One of the first studies to demonstrate that PTH can prevent fractures was published in 2001.<sup>6</sup> This was a randomized trial of 1,637 postmenopausal women with a prior vertebral fracture. The women were randomized to receive placebo, 20 mg of PTH subcutaneously once a day, or 40 mg of PTH subcutaneously once a day for 2 years. The outcomes included BMD, vertebral, and nonvertebral fractures. The average age of the subjects was 71 years, with a T spine score of -2.6. Approximately 30% had 1 vertebral fracture and approximately 60% had  $\geq 2$  vertebral fractures. Investigators found that PTH, at a dose of 20 mg/day, reduced the risk of new vertebral fractures and nonvertebral osteoporotic fractures by 65% and 53% respectively, and increased spine and femoral neck BMD by 10% and 3%, respectively. There were no differences in adverse events among patients randomized to PTH compared with those randomized to placebo.

The fact that PTH is an anabolic agent has led to the question of whether it can and should be used with

**Table 3: Practical points: parathyroid hormone (PTH)**

- It is the only anabolic agent currently available in Canada.
- Its use is associated with increased BMD and decreased incidence of fracture.
- It is safe, with minimal side effects.
- Consider its use as a single agent in patients who have fractured on antiresorptive therapy or cannot tolerate anti-catabolic therapy.
- Cost (approximately \$15,000 for 18 months) may limit use.

BMD = bone mineral density

an anti-catabolic. The data on combination therapy are minimal, but it is known that concurrent therapy with bisphosphonates blunts the anabolic effect of PTH; therefore, it is better to prescribe sequential combinations. The anabolic actions of PTH with other anti-catabolics before, during, or after PTH are not known and require further study. PTH is typically prescribed in doses of 20 mg subcutaneously once daily and can be given for up to 18 months.

**Which patients would benefit from PTH therapy?** The Canadian product monograph for PTH suggests that it would be appropriate for postmenopausal women with severe osteoporosis, who are at high risk of fracture or who have failed or are intolerant to other therapies. It can be used to increase bone mass in men with primary or hypogonadal osteoporosis, who have failed or are intolerant to other therapies. It should be noted that the effects of PTH on risk for fracture in men have not yet been demonstrated

PTH is contraindicated in patients with bone metastases; a history of skeletal malignancies; metabolic bone disease; pre-existing hypercalcemia; renal impairment (ie, creatinine clearance [CrCl] < 30 mL/min); Paget's disease of bone or unexplained elevations of alkaline phosphatase; patients with prior radiation therapy (external beam or implant) involving the skeleton; and in children or young adults with open epiphyses. Table 3 summarizes practical points concerning PTH.

### Denosumab

RANKL, a protein expressed by osteoblastic stromal cells, binds to the receptor activator of NF $\kappa$ B (RANK) and is the primary mediator of osteoclast differentiation, activation, and survival. RANKL is

**Table 4: Practical points: denosumab**

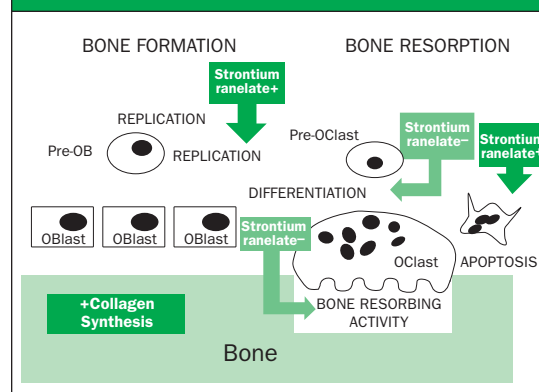
- Denosumab SC at 3 months or 6 months (60 mg) increases lumbar spine BMD over 12 months.
- There is a rapid onset of action as indicated by bone turnover markers.
- No difference in adverse events compared with placebo.
- Further investigation is warranted.

responsible for osteoclast-mediated bone resorption in a broad range of conditions. OPG, a soluble RANKL decoy receptor that binds RANKL, is the key endogenous regulator of the RANKL-RANK pathway. This pathway is illustrated in Figure 1.

Denosumab is a fully monoclonal antibody that binds to RANKL with high affinity and specificity, and blocks the interaction between RANKL and RANK, mimicking the endogenous effects of OPG. A recent phase 2 study reported on the efficacy and safety of denosumab in 412 postmenopausal women with low BMD, who were followed for 12 months.<sup>7</sup> Subjects were randomly assigned to denosumab, either every 3 months (at a dose of 6, 14, or 30 mg) or every 6 months (at a dose of 14, 60, 100, or 210 mg), open-label oral alendronate (70 mg weekly), or placebo. The primary outcome was the percentage change from baseline in spine, hip, and distal radius BMD for each group. Secondary outcomes included changes in bone turnover markers and adverse events. Denosumab increased spine BMD by 3.0% to 6.7%, total hip BMD by 1.9% to 3.6%, and radial BMD by 0.4% to 1.3%. Increases in BMD with denosumab were superior to those with placebo, and similar to or greater than those with alendronate. Markers of bone resorption decreased as early as 2 months in the denosumab group and, compared with placebo, there was no difference in types and rates of adverse events. These preliminary findings suggest that denosumab might be an effective treatment for osteoporosis. Table 4 summarizes practical points concerning denosumab.

### Strontium ranelate

Strontium ranelate has recently been licensed in Europe for the treatment of osteoporosis. The mechanism of action for strontium ranelate is not

**Figure 3: The site of action of strontium ranelate**

Adapted from Marie PJ, et al.<sup>8</sup>

yet fully understood, but compared with other currently available treatments, it seems to have the unique ability to both inhibit bone resorption and stimulate bone formation.<sup>8</sup> Figure 3 illustrates the sites at which strontium ranelate is thought to act.

There have been 2 international, double-blind, placebo-controlled studies on the effects of strontium ranelate, 2 g/day. The Spinal Osteoporosis Therapeutic Intervention (SOTI) trial enrolled 1,649 postmenopausal women with low BMD and at least 1 vertebral fracture to strontium ranelate or placebo for 3 years.<sup>9</sup> This trial demonstrated that new vertebral fractures occurred in fewer patients in the strontium ranelate group compared with the placebo group (relative risk reduction: 0.59; 95% confidence interval [CI], 0.48 to 0.73). There were no significant differences between the groups in the incidence of serious adverse events. The Treatment of Peripheral Osteoporosis (TROPOS) study enrolled 5,091 postmenopausal women with osteoporosis and assessed the efficacy of strontium ranelate, compared with placebo, in preventing nonverte-

**Table 5: Practical points: strontium ranelate**

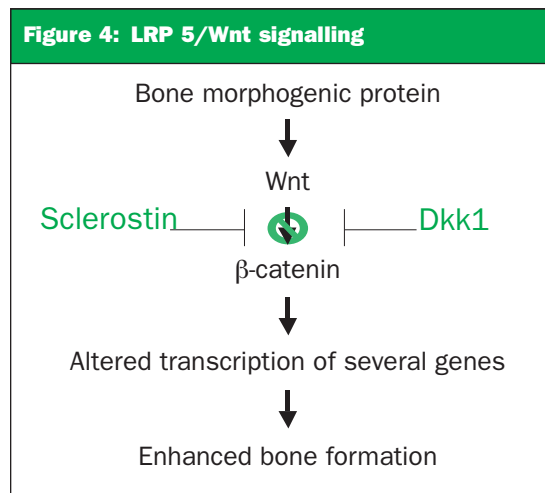
- It is the first agent that has dual effects on bone remodeling.
- It permanently binds to bone and increases BMD; thus, DXA reports must be corrected for strontium
- The effects of health food supplements that contain strontium on BMD and/or fractures are not known.

DXA = dual energy x-ray absorptiometry

bral fractures.<sup>10</sup> Strontium ranelate decreased non-vertebral fractures (eg, hip, pelvis, sacrum, clavicle, and humerus) by 18% ( $p=0.031$ ) and significantly reduced the risk of hip fracture (36%;  $p=0.046$ ) in a subset of women at high risk. Strontium ranelate is currently under review at Health Canada. Table 5 summarizes practical points concerning strontium ranelate.

### Sclerostin

Sclerosteosis is a rare disease (reported in <100 men and women) due to a deficiency in sclerostin. Patients with sclerosteosis have hyperostosis, a thickening of the skull, mandible, ribs, all long bones, and a large stature, as well as, facial nerve palsy, hearing loss, atrophy of the optic nerve, and syndactyly.<sup>11</sup> Research in patients with sclerosteosis has led to the identification of sclerostin, an inhibitor of bone formation. Sclerostin is made by osteocytes, the cells found in bone matrix. Osteocytes form a cellular network throughout the bone allowing them to communicate with each other and the bone-lining cells. While the exact role of osteocytes is still under investigation, it is likely that they direct bone remodeling to accommodate mechanical strain and repair fatigue damage. Sclerostin inhibits bone formation by inhibiting bone morphogenic protein (BMP)-stimulation of osteoblasts by antagonizing Wnt signalling (Figure 4).<sup>11</sup> Animal studies have demonstrated that treatments aimed at inhibiting sclerostin increase bone mass by up to 4% compared with controls.<sup>12,13</sup> Trials of sclerostin in humans are ongoing and practical points regarding sclerostin are found in Table 6.



**Table 6: Practical points: sclerostin**

- Diseases of bone metabolism may provide therapeutic insights.
- The osteocyte is important in understanding bone cell communication.
- Further study of the Wnt pathway may lead to the development of other agents for the prevention and treatment of osteoporosis.

### Summary

In the past 10 years, there has been an increase in the number and types of osteoporosis treatments. One of the most significant advances has been the development of anabolic agents such as PTH. Over the next 10 years, our understanding of the complex physiology of bone remodeling will increase and, associated with this increase, there will be development of more targeted treatments for osteoporosis. Ongoing investigations to identify new treatments for osteoporosis are critical, since this will increase treatment options and may result in the development of more effective therapies. Ultimately, these developments will help to reduce the number of men and women with osteoporosis.

### References

1. Katagiri T, Takahashi N. Regulatory mechanisms of osteoblast and osteoclast differentiation. *Oral Dis* 2002;8(3):147-159.
2. Blair HC, Zaidi M, Schlesinger PH. Mechanisms balancing skeletal matrix synthesis and degradation. *Biochem J* 2002; 364(Pt 2):329-341.
3. Chae HJ, Park RK, Chung HT, et al. Nitric oxide is a regulator of bone remodelling. *J Pharm Pharmacol* 1997;49(9):897-902.
4. Collin-Osdoby P, Nickols GA, Osdoby P. Bone cell function, regulation and communication: a role for nitric oxide. *J Cell Biochem* 1995;57:399-408.
5. Cummings SR, Cosman F, Jamal SA, eds. Osteoporosis: An evidenced-based guide to prevention and management. Philadelphia: American College of Physicians; 2002. Charney P, ed. Women's Health Series.
6. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344: 1434-1441.
7. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006;354:821-831.
8. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. *Calcif Tissue Int* 2001;69(3):121-129.
9. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350(5):459-468.

10. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90:2816-2822.
11. Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet* 2001;10(5):537-543.
12. van Bezooijen RL, Roelen BA, Visser A, et al. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. *J Exp Med* 2004;199(6):805-814.
13. van Bezooijen RL, Svensson JP, Eefting D, et al. Wnt but not BMP signaling is involved in the inhibitory action of sclerostin on BMP-stimulated bone formation. *J Bone Miner Res* 2007; 22(1):19-28.
14. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003;423(6937):337-342.

## Abstract of Interest

### Wnt but not BMP signaling is involved in the inhibitory action of sclerostin on BMP-stimulated bone formation.

VAN BEZOOIJEN RL, SVENSSON JP, EEFING D, ET AL. LEIDEN, THE NETHERLANDS.

Sclerostin is an osteocyte-derived negative regulator of bone formation. It inhibits BMP-stimulated bone formation both in vitro and in vivo but has no direct effect on BMP signaling. Instead, sclerostin inhibits Wnt signaling that is required for BMP-stimulated osteoblastic differentiation.

**INTRODUCTION:** Sclerostin is a member of the Dan family of glycoproteins of which many members have been reported to antagonize BMP activity. Sclerostin has been shown to inhibit BMP-stimulated bone formation, but its mechanism of action seems to be different from classical BMP antagonists. In this study, we investigated the mechanism by which sclerostin inhibits BMP-stimulated bone formation.

**MATERIALS AND METHODS:** DNA electroporation of calf muscle of mice using expression plasmids for BMP and sclerostin was used to study the effect of sclerostin on BMP-induced bone formation in vivo. Transcriptional profiling using microarrays of osteoblastic cells treated with BMP in the absence or presence of sclerostin was used to find specific growth factor signaling pathways affected by sclerostin. The affected pathways were further studied using growth factor-specific reporter constructs.

**RESULTS:** BMP-induced ectopic bone formation in calf muscle of mice was prevented by co-expression of sclerostin in vivo. Transcriptional profiling analysis of osteoblastic cultures indicated that sclerostin specifically affects BMP and Wnt signaling out of many other growth signaling pathways. Sclerostin, however, did not inhibit stimulation of direct BMP target genes. Furthermore, we did not obtain any evidence for sclerostin acting as a direct BMP antagonist using a BMP-specific reporter construct. In contrast, sclerostin shared many characteristics with the Wnt antagonist dickkopf-1 in antagonizing BMP-stimulated bone formation and BMP- and Wnt-induced Wnt reporter construct activation.

**CONCLUSIONS:** Sclerostin inhibits BMP-stimulated bone formation but does not affect BMP signaling. Instead, it antagonizes Wnt signaling in osteoblastic cells. High bone mass in sclerosteosis and van Buchem disease may, therefore, result from increased Wnt signaling.

*J Bone Miner Res* 2007;22(1):19-28.

## Upcoming Scientific Meetings

24-27 October 2007

### 11<sup>th</sup> Annual Canadian Diabetes Association/ Canadian Society of Endocrinology and Metabolism (CDA/CSEM) Professional Conference

Vancouver Convention and Exhibition Centre,  
British Columbia  
CONTACT: Website: [www.diabetes.ca/conference](http://www.diabetes.ca/conference)

3-7 November 2007

### American Heart Association 2007

Orlando, Florida  
Orange County Convention Center  
CONTACT: <http://aha.orlandomeetinginfo.com>

1-3 February 2008

### 55<sup>th</sup> Annual Advanced Postgraduate Course

American Diabetes Association  
San Francisco, California  
CONTACT: [http://professional.diabetes.org/  
Congress\\_Display.aspx?TYP=9&CID=57416](http://professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=57416)

**Disclosure Statement:** Dr. Jamal has stated that she has no conflicts of interest to disclose in association with the contents of this issue.

Change of address notices and requests for subscriptions to *Endocrinology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to [info@snellmedical.com](mailto:info@snellmedical.com). Please reference *Endocrinology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

sanofi-aventis