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COMMENTARIES

The Promise of Sclerostin Inhibition for the Treatment of Osteoporosis

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Commentary on: Li X, Ominsky MS, Warmington KS, Morony S, Gong J, Cao J, Gao Y, Shalhoub V, Tipton B, Haldankar R, Chen Q, Winters A, Boone T, Geng Z, Niu QT, Ke HZ, Kostenuik PJ, Simonet WS, Lacey DL, Paszty C. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. *J Bone Miner Res*. 2009 Apr;24(4):578-88.

A lack of sclerostin expression in mature osteocytes results in a progressive, generalized, massive bone mass increase due to high bone formation in humans and mice (1-3), suggesting that inhibition of this secreted glycoprotein might restore bone mass and thus strength to the osteoporotic skeleton. The present study by Paszty *et al*. (4) demonstrates that, indeed, bi-weekly, subcutaneous treatment with 25 mg/kg of a sclerostin function-blocking antibody for 5 weeks rebuilds bone mass in aged, estrogen-deprived, osteoporotic rats. Bone gain was related to impressive increases in the amount of bone-forming and mineralizing surfaces and in bone matrix deposition at all skeletal envelopes, while bone resorption was not elevated. As a result, bone strength was improved in the axial and appendicular skeleton. Sclerostin, which was originally described as a BMP antagonist (5), is currently thought to function as a paracrine inhibitor of canonical Wnt signaling in osteoblasts by binding to the Wnt co-receptors LRP5 and 6 (6-8), although recent evidence from mouse genetic studies suggests that LRP5 might rather control bone formation by inhibiting serotonin synthesis in the duodenum (9).

Hence the current study provides an impressive demonstration that inhibition of sclerostin results in bone mass restoration in the aged, osteoporotic, mammalian skeleton and this approach therefore holds great potential for the treatment of osteoporosis. However, further research is required to elucidate the underlying mode of action.

Most osteoporosis treatments stop bone loss by inhibiting bone resorption but cannot rebuild bone mass. Reduction in hip fracture risk reaches only around 40% even with the most efficacious treatments (10). The only available bone-forming therapy involves daily subcutaneous injection of parathyroid hormone (PTH) 1-84 or the PTH fragment 1-34, making treatment cumbersome. Furthermore, over time, this treatment increases not only bone formation but also bone resorption, resulting in high bone turnover (11). Consequently, a bone-building therapy that does not require daily injections, increases bone formation without increasing bone resorption and thus bone turnover, and has improved efficacy with respect to reduction of hip fracture risk is highly desirable.

Inhibition of osteocyte-secreted sclerostin by an antibody appears to fit this profile. While this has been hypothesized since the discovery of sclerostin as a key inhibitor of bone formation based on human and mouse genetic studies (1-3), it had not been proven to date in a published paper. The present rodent study (4) provides supportive evidence, since the anti-sclerostin antibody induces bone formation at cancellous and endocortical bone sites, at the limited intracortical bone remodeling sites present in aged, estrogen-deprived rodents, and at

the subperiosteal bone envelope. The overall effects on cortical bone are particularly encouraging for the clinic, since observational studies suggest that hip fractures are associated predominantly with a poor cortical bone template and increased intracortical porosity (12).

The bone-forming effects of the anti-sclerostin antibody resemble, in some ways, those of high dose, intermittent PTH treatment in rodents (13). Consistent with this observation, *SOST*, the gene encoding sclerostin, is transcriptionally regulated by intermittent PTH treatment (14;15). Its transient suppression appears to mediate some aspects of PTH's bone-forming properties, since anabolic responses are blunted but not abolished in mice with aberrant sclerostin levels (16).

Nonetheless, there are also some differences in the pattern of bone gain elicited by each treatment. While all skeletal envelopes respond to bone anabolic intermittent PTH treatment, those adjacent to bone marrow are most responsive, whereas the subperiosteal envelope appears less reactive (13). It was speculated that this might relate in part to the limited cellular activity at this envelope and/or a requirement of some resorptive activity for a full PTH bone anabolic effect, which is mediated in part by mechanisms based on remodeling. In the present study (4), inhibition of sclerostin resulted in robust bone-forming responses at subperiosteal bone surfaces, though some prevalence of endocortical and cancellous bone effects was observed nevertheless. This pattern of bone gain suggests that the treatment triggers modeling-based bone anabolic responses in the aged mammalian skeleton, which is otherwise maintained primarily by remodeling. Since subperiosteal bone formation was demonstrated to take place in the aged human femoral neck (17), it is tempting to speculate that stimulation of bone anabolism at this skeletal envelope by sclerostin inhibition might contribute to reduction of fracture risk at this site, since even modest increases in bone radius will improve bone strength considerably (18).

Most importantly, the marked increases in bone formation induced by the anti-sclerostin antibody are not associated with increases in bone resorption, at least in the present short-term study (4). It remains to be seen whether the described suppression of cancellous bone resorption is of any relevance in longer-term therapy. A putative direct or indirect impact of sclerostin inhibition on bone resorption requires further investigation. Studies in sclerostin-deficient humans (sclerosteosis, OMIM 269500 and van Buchem disease, OMIM 239100) and mice did not point towards a major effect (1-3;19). Overall, the present data therefore indicate that sclerostin inhibition-induced bone formation increases are not linked to elevated bone remodeling in the aged rodent skeleton. For short-term, intermittent PTH treatment such uncoupling of bone resorption and formation and direct modeling-based bone formation have also been demonstrated (11). Yet, longer-term treatment is clearly characterized by increases in bone resorption and bone remodeling (11).

Based on amino acid sequence similarity, sclerostin was originally thought to act as a bone morphogenetic protein (BMP) antagonist in adult bone and was indeed shown to bind weakly to BMPs and to thereby inhibit BMP signaling at high doses (5). Subsequent *in vitro* studies demonstrated that sclerostin binds to the Wnt co-receptors low-density lipoprotein receptor-related protein (LRP) 5 and 6 (6;7). Therefore, sclerostin is currently thought to inhibit osteoblastic canonical Wnt signaling, which has been implicated in bone mass regulation (8). This hypothesis is supported by the phenotypic overlap between human bone overgrowth disorders related to loss-of-function mutations in *SOST* and gain-of-function mutations in *LRP5,* and the observation that sclerostin binding is decreased to the mutated form of *LRP5* associated with the high bone mass phenotype (20). However, conclusive *in vivo* proof for this hypothesis must still be provided, especially after the recent and unexpected finding in mice that *Lrp5* might act not so much as a local Wnt signaling mediator in bone but rather to control osteoblastic proliferation in a non-cell-autonomous fashion by inhibiting serotonin synthesis in the duodenum (9). If true, this

would be difficult to reconcile with mediation of sclerostin's mode of action, unless data become available that osteocyte-secreted sclerostin is circulating in substantial amounts and does not act as a local bone formation regulator but rather by binding to LRP5 in the gut and thus regulating serotonin levels.

On the other hand, it has not been formally proven yet whether the assumption that sclerostin acts as a paracrine factor on osteoblasts is correct (8). At present it can also not be excluded that sclerostin has some autocrine action on mature osteocytes that express sclerostin once they are entrapped within mineralized matrix (21;22), especially since preliminary data suggest that canonical Wnt signaling in osteocytes is relevant for bone mass regulation (23). If true, this would suggest that other factors might be regulated downstream of sclerostin in these cells, which in turn control bone formation. Osteocytes are interconnected with each other, with osteoblasts and with lining cells via dendritic processes forming a communication network throughout the bone matrix and to the bone surface that seems ideally suited for sensing and responding to the needs of the skeleton. Indeed it has long been hypothesized that osteocytes mediate bone adaptation to mechanical strain, a theory that is supported by recent evidence demonstrating that ablation of osteocytes results in lack of responsiveness of the skeleton to strain (24). Interestingly, sclerostin expression decreases following mechanical strain that is bone anabolic (25), while unloading appears to increase its expression (25;26). This suggests that sclerostin suppression might be required to enable local bone-forming responses to mechanical strain. If true, blocking sclerostin action might remove a regulator that keeps local osteogenesis in check so it is in alignment with prevailing loads. Preliminary evidence by Paszty and colleagues shows that at least part of the bone gained during anti-sclerostin antibody treatment is swiftly lost following cessation of treatment (27). These data might indicate that excess bone not required for prevailing loads is removed upon relief of sclerostin blockage. They also demonstrate that bone gained due to sclerostin inhibition will require maintenance with an anti-resorptive principle as has been shown for PTH-induced bone gain (12).

The authors of the present study do not refer to the binding characteristics of the present antibody to sclerostin or to its pharmacokinetic profile, nor do they show any dose-effect relation, making it not possible to judge whether frequent high dose applications were chosen due to antibody characteristics or if they were required for achievement of bone anabolic effects of such an impressive magnitude because of sclerostin biology. Limited circumstantial evidence hints at (a) sclerostin being generated in high amounts within mineralized bone (25) and (b) presumably relatively modest anabolic responses following partial sclerostin suppression, since humans lacking one allele of *SOST* display only mild bone overgrowth (1;2).

Finally, the authors note that sclerostin inhibition induces deposition of normal lamellar bone consistent with observations in humans and mice lacking sclerostin (1-3). One question that is not addressed in the current short-term study is whether sclerostin inhibition impacts bone tissue mineralization. Mechanical testing of *Sost*-deficient mouse bones indicates that any putative changes would presumably not negatively affect bone strength (3). Likewise, we will have to wait for further detailed long-term studies to determine whether sclerostin inhibition has side effects. Information from patients lacking sclerostin suggests that complications such as facial nerve palsy (1;2) could occur due to the excessive bone formation, and these complications need to be addressed following chronic treatment. Along those lines, the authors of the present paper (4) do not provide any insight on anti-sclerostin antibody-induced bone changes in the skull, a prominent site for abnormal bone growth in patients lacking sclerostin (1;2). To date there is no conclusive evidence about potential effects of sclerostin inhibition outside the skeletal system, though low level sclerostin expression has been reported in a few other organ systems such as the vascular system (28;29) and the kidney (1;14). Finally recent data suggest that attention needs to be paid to putative

changes in osteosarcoma susceptibility when de-repressing the Wnt pathway in bone by inhibiting local Wnt antagonists such as presumably sclerostin (30).

In summary, the results of the present study give rise to hope that treatments based on inhibition of sclerostin activity could provide a powerful way to restore bone strength of the osteoporotic skeleton, potentially providing more efficacious protection from hip fractures than current therapies. As with PTH, which was discovered empirically to have anabolic effects on bone and continues to be an intensive area of research with respect to its specific mechanisms of action, much remains to be learned as to precisely how inhibition of sclerostin promotes bone formation.

Conflict of Interest: Dr. Kneissel reports that she is an employee of Novartis Institutes for BioMedical Research.

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