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**Effects of sclerostin antibody on bone healing**

Mihara A *et al*. Scl-Ab and bone healing

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**Abstract**

Promoting bone healing after a fracture has been a frequent subject of research. Recently, sclerostin antibody (Scl-Ab) has been introduced as a new anabolic agent for the treatment of osteoporosis. Scl-Ab activates the canonical Wnt (cWnt)-β-catenin pathway, leading to an increase in bone formation and decrease in bone resorption. Because of its rich osteogenic effects, preclinically, Scl-Ab has shown positive effects on bone healing in rodent models; researchers have reported an increase in bone mass, mechanical strength, histological bone formation, total mineralized callus volume, bone mineral density, neovascularization, proliferating cell nuclear antigen score, and bone morphogenic protein expression at the fracture site after Scl-Ab administration. In addition, in a rat critical-size femoral-defect model, the Scl-Ab-treated group demonstrated a higher bone healing rate. On the other hand, two clinical reports have researched Scl-Ab in bone healing and failed to show positive effects in the femur and tibia. This review discusses why Scl-Ab appears to be effective in animal models of fracture healing and not in clinical cases.

**Key Words:** Canonical Wnt-β-catenin pathway; Fracture healing; Osteoporosis; Romosozumab; Sclerostin antibody

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**Core Tip:** Sclerostin antibody (Scl-Ab) has been recently introduced for the treatment of osteoporosis. Several researchers have reported on the effects of Scl-Ab in bone fracture healing because of its rich osteogenic potential. In this review, we describe the latest reports of preclinical and clinical studies on the bone-healing effects of Scl-Ab.

**INTRODUCTION**

Achieving robust bone healing is the ultimate goal in the treatment of bone fractures. The development of methods to promote fracture healing has been a frequent subject of research. Recently, the safety of several osteoporosis drugs has been established in large-scale clinical trials, and it is expected that these drugs could be converted to fracture treatment. In experimental studies, some agents used to treat osteoporosis have had a positive effect on the promotion of bone healing, including parathyroid hormone (PTH), bisphosphonates, and sclerostin antibody (Scl-Ab).

Romosozumab, an Scl-Ab for humans, which recently has been developed for the treatment of osteoporosis, is an anabolic agent that stimulates bone formation. The difference between Scl-Ab and PTH1-34 (teriparatide), a former anabolic agent, is that teriparatide increases both bone formation and resorption *via* PTH-PTH receptor signaling, whereas Scl-Ab increases bone formation and simultaneously decreases bone resorption *via* canonical Wnt (cWnt)-β-catenin signaling[1]. This difference shows that the bone formation by PTH1-34 is primarily “remodeling-based” and that by Scl-Ab is primarily “modeling-based”[2,3].

In this review, we describe how Scl-Ab effects the cWnt-β-catenin pathway to stimulate bone formation and then discuss the current experimental and clinical evidence in bone healing.

**Sclerostin and the canonical Wnt**/**BETA-catenin pathway in bone metabolism**

The cWnt-β-catenin pathway plays an important role in bone metabolism, including skeletal development and homeostasis and bone remodeling[4]. The pathway is activated by the binding of Wnt proteins to receptor complexes composed of frizzled receptors and co-receptors of the low-density lipoprotein receptor-related protein (LRP) family, LRP5 and LRP6. This event increases the level of β-catenin and induces its translocation to the nucleus and activates the transcription of gene; it further accelerates the differentiation of osteoblast precursors and promotes the maturation of osteoblast and their survival, leading to osteogenesis by the increased and activated osteoblasts. On the other hand, the increased level of β-catenin results in an increased expression of osteoprotegerin, which binds to RANKL as a decoy receptor, preventing the binding of RANKL and RANK. Osteoclast activation and differentiation, which lead to bone resorption, occurs in the presence of RANKL-to-RANK binding. Thus, the activation of this pathway leads to increased bone formation by the increased and activated osteoblasts and to decreased bone resorption due to the disturbed binding of RANKL to RANK[5-7].

In the regulation of the cWnt-β-catenin pathway, osteocytes play an important role as producers and targets of Wnt ligands and as secretors of molecules that regulate Wnt action[8]. One regulation mechanism is the secretion of sclerostin, a potent antagonist of Wnt signaling. Sclerostin is a protein encoded by the *SOST* gene primarily expressed by mature osteocytes, but not by early osteocytes or osteoblasts[9]. Sclerostin binds to the Wnt co-receptors LRP5/LRP6, antagonizing downstream signaling in the cWnt-β-catenin pathway[10]. Thus, when the stoichiometry levels of sclerostin overwhelms the levels of the Wnt ligands, the signals will not be activated, leading to β-catenin degradation, lower bone formation, and higher bone resorption. On the other hand, when the stoichiometry levels favor in Wnt ligands than sclerostin, Wnt-β-catenin signaling will be activated, leading to stabilized β-catenin for translocation to the nucleus and the activation of target genes to increase bone formation and decrease bone resorption[2]. In addition, not only LRP 5 and 6, but also LRP4 was associated with bone homeostasis by interacting with sclerostin; mutation of LRP4, impairing interaction with sclerostin was found in patients suffering from bone overgrowth[11]. Thus, sclerostin is established as a bone formation inhibitor, though the molecular mechanisms are not fully understood.

In humans, the absence of sclerostin expression or secretion causes an abnormally high bone mass. These conditions have been seen in the rare hereditary diseases sclerosteosis and van Buchem disease. Sclerosteosis was first described by Truswell as osteopetrosis with syndactyly and is mostly seen in patients in South Africa; van Buchem disease was described by van Buchem as hyperostosis corticalis generalisata familiaris and is mostly found in patients in the Netherlands[12,13]. In both diseases, the *SOST* gene encoding sclerostin was identified as the gene responsible; a loss-of-function mutation occurs in sclerosteosis, and the downregulation of the expression of the *SOST* gene occurs in van Buchem disease[14]. Bone mineral density (BMD) and bone strength are significantly higher in patients with these diseases than those in the general population[15,16]. In experimental reports using mice, genetic deletion of the *SOST* gene or neutralizing antibodies for sclerostin duplicated the high bone mass found in humans lacking sclerostin[17-19]. Conversely, sclerostin overexpression leads to a decrease in bone mass[20-22].

**SCLEROSTIN ANTIBODY THERAPY AND OSTEOPOROSIS**

As the mechanisms of sclerostin and the cWnt-β-catenin pathway were elucidated, improvement in bone mass became the expected outcome of inhibiting the action of sclerostin. In a study using a model of ovariectomized rats with postmenopausal osteoporosis treated with Scl-Ab, researchers found a significant increase in bone formation on the trabecular, periosteal, endocortical, and intracortical surfaces. Furthermore, osteoblast and mineralizing surfaces increased, while the osteoclast surface decreased. These results suggest that the use of Scl-Ab increased bone formation and decreased bone resorption for osteoporosis[23].In another study evaluating the effects of the osteoblast lineage in young rats with Scl-Ab and PTH1-34, the osteoblastic surface and estimated total number of osteoblasts increased to similar levels in both the Scl-Ab and PTH1-34 groups at week 4. However, both parameters decreased in the Scl-Ab group while maintaining in the PTH1-34 group at week 26. Similarly, the osteoprogenitors increased to similar levels in both groups at week 4, and only those in the Scl-Ab group decreased at week 26. Interestingly, the percentage of labeled perimeter of the periosteal surface of the femur diaphysis was higher in the Scl-Ab group at both weeks 4 and 26, and the percentage of labeled perimeter of the endocortical surface was at the same level at week 4 and was higher in the Scl-Ab group at week 26. These results suggest that Scl-Ab strongly increases the differentiation induction of osteoprogenitors to osteoblasts, while increase of osteoprogenitors are only seen in the early stages of administration. While, PTH1-34 increases both the differentiation induction of osteoprogenitors to osteoblasts and the number of osteoprogenitors at similar levels throughout the administration period, although the level of bone formation was similar or even higher in Scl-Ab than in PTH1-34[24].

In cynomolgus monkeys, treatment with Scl-Ab led to increase in BMD and bone strength just like in the rats. No increase in bone resorption markers was noted, while a significant increase in bone formation markers was demonstrated, also suggesting the distinct effects of modeling-based bone formation associated with Scl-Ab, differing from remodeling-based bone formation by PTH1-34 in which osteoblast-mediated bone formation follows osteoclast-mediated bone resorption[25]. Summarizing the difference between Scl-Ab and PTH, with Scl-Ab, bone formation is seen with no increase or even some decrease of bone resorption. The effect of bone formation is stronger in the early stages of administration and decreases with longer administration due to lack of osteoprogenitors after the strongly accelerated differentiation to osteoblasts. With PTH, bone formation is also seen with increase of bone resorption (relatively higher formation than resorption). Bone formation is similar in any stage of administration due to increase in both number of osteoprogenitors and differentiation to osteoblasts.

Romosozumab, a Scl-Ab agent for humans, has recently become commercially available for clinical use. A phase III clinical trial has shown that romosozumab strengthened osteoporotic bone by increasing BMD and decreased the incidence of new fractures. The Fracture Study in Postmenopausal Women with Osteoporosis trial evaluated the 12-month efficacy of romosozumab as compared with the placebo. The risk of vertebral fracture was reduced by 73% at 12 mo (incidence, 0.5% in the romosozumab group *vs* 1.8% in the placebo group, *P* < 0.001), and the risk of clinical fracture was reduced by 36% at 12 mo (incidence, 1.6% in the romosozumab group *vs* 2.5% in the placebo group, *P* = 0.008). The percentage of change in BMD from baseline was 13.3% greater in the lumbar spine, 6.9% greater in the total hip, and 5.9% greater in the femoral neck in the romosozumab group than in the placebo group. An increase in the bone formation marker P1NP was seen in the romosozumab group, and a decrease in the bone resorption marker β-CTX was seen early in treatment, suggesting modeling-based bone formation[26]. Similar results of increased bone formation and strength, decreased fracture risk, and increased levels of bone formation markers with decreased levels of bone resorption markers have been shown in other phase III trials (ARCH trial, romosozumab *vs* alendronate; STRUCTURE trial, romosozumab *vs* teriparatide)[1,27].

**SCLEROSTIN ANTIBODY THERAPY AND BONE HEALING**

***Preclinical evidence***

Bone healing is a complex process controlled by numerous cellular signaling pathways regulated by factors expressed in a time and concentration-dependent manner. The cWnt-β-catenin pathway is one of the most critical signaling pathways involved in bone healing[28-30]. The peak of upregulation was from 7 to 14 d in rat models[31,32]. Upregulating and/or controlling the cWnt pathway along with the levels of β-catenin have the potential of accelerating bone healing. Bone healing occurs in two different mechanisms; intramembranous or endochondral bone formation. Marsell *et al*[33] reported Wnt-responsive cells were not observed near the marrow cavity but seen over the periosteal callus, presuming that the cWnt-β-catenin pathway associates with endochondral bone formation rather than intramembranous bone formation. Liedert *et al*[34] suggested that Wnt inhibitors play a role in delayed union and Montjovent *et al*[35] demonstrated non-rigid fixation of femoral defects caused increase levels of inhibitors of Wnt proteins. In non-rigid fixation, endochondral bone formation becomes the main healing process. Inhibiting the inhibitors of Wnt proteins and activating the cWnt-β-catenin pathway may help bone healing in such fractures.

The efficacy of Scl-Ab for bone healing has been demonstrated in several reports with animal models (Table 1). In a mouse tibial-shaft osteotomy model, both the sclerostin knockout and wild-type groups showed an increase in bone mass at the osteotomy site when Scl-Ab was administered[36]. Ominsky *et al*[37] observed in a rat femur fracture model that an increase in bone mass and mechanical strength at the fracture site occurred after 7 wk in the Scl-Ab group. The other researchers also reported similar positive effects of Scl-Ab for a rat femur fracture or osteotomy model[38,39]. Virdi *et al*[40] also observed that in a rat femoral bone ablation model with intramedullary fixation, there was a 1.9-fold increase in fixation strength at week 4 and a 2.2-fold increase at week 8 in the Scl-Ab group compared to the vehicle group. Furthermore, Yee *et al*[41] reported in a type 1 diabetes mellitus (T1DM) mouse model, administration of Scl-Ab mitigates inhibition of osteoblast differentiation caused by the diabetic state. They found a significant benefit in callus bone volume, increase in callus size and a reverse of lower mineralization seen in T1DM mouse model. Studying the mechanisms for the fracture healing effect of Scl-Ab, Feng *et al* reported an increase in the proliferating cell nuclear antigen score and bone morphogenetic protein (BMP)-2 expression at weeks 1 and 2 in a femur osteotomy model in young rats. Furthermore, cartilage decreased and BMD and the mechanical strength of the callus associated with accelerated fracture healing increased at weeks 4 and 6[42].

As an evaluation outside the long tubular bone fracture model, Agholme *et al*[43] inserted screws into the proximal tibia of young rats and measured the pull-out strength; the Scl-Ab-treated group showed a 50% increase after 2 and 4 wk compared with the saline-treated group. They conducted the same experiment comparing with PTH, and the PTH group showed significant higher pull-out strength in the metaphyseal, while Scl-Ab significantly increased femoral cortical and vertebral strength[44]. In a rat model of distraction osteogenesis, no difference occurred in the rate of bone union between the Scl-Ab and control groups, but mechanical strength and bone mass increased in the Scl-Ab group, suggesting that the optimal effect of Scl-Ab treatment is achieved in the later stages of distraction osteogenesis[45]. In addition, in a rat critical-size femoral-defect model with a 6-mm femoral defect, 24% of the Scl-Ab-treated group had healed after 12 wk compared with no cases of healing in the control group[46]. Furthermore, in the treated group, systemic Scl-Ab administration plus local BMP-2 administration resulted in significantly more robust healing of critical-size femoral defects than did BMP-2 alone[47].

On the other hand, Kruck *et al*[48] negatively reported on the effects of Scl-Ab on bone healing. The author created rigid and semirigid fixation models for femoral osteotomy in rats. All groups showed an increase in bone mass, but no difference in delayed healing occurred with semirigid fixation between the Scl-Ab and control groups. In rigid fixation, Scl-Ab had more bridging of the endosteum, which adversely affected late healing, suggesting delayed callus remodeling and marrow reconstitution at the time of fracture. These results suggest that Scl-Ab promotes bone formation in the early stages of healing, but not in the advanced stages of fracture callus remodeling[48].

***Clinical evidence***

Two phase II clinical trials have reported the efficacy of romosozumab in adult fresh fractures. Bhandari *et al*[49] reported the efficacy of romosozumab in 402 patients with fresh unilateral tibial diaphyseal fractures (median age, 40 years; range, 18−82 years) who underwent fracture fixation with intramedullary nails. Patients were randomized to a placebo (*n* = 103) or one of nine different romosozumab groups (*n* = 299), with three different doses and frequencies of administration (doses: 70 mg, 140 mg, and 210 mg; administration: twice, postoperative day 1 and week 2; three times, postoperative days 1 and 2 and week 6; and four times, postoperative days 1 and 2 and weeks 6 and 12). The percentage of patients with a radiological cure, defined as the bridging of three of the four cortices as shown on the radiographs, which ranged from 63.2% to 84.7% at week 24 and from 83.4% to 96.7% at week 52 in the romosozumab group and from 76.1% at week 24 and 87.1% at week 52 in the placebo group. The estimated median time to radiological cure ranged from 14.4 to 18.6 wk in the romosozumab group and 16.4 wk in the placebo group. Thus, no significant difference occurred between both groups. In addition, no significant difference occurred in the time to clinical healing (defined as the ability to bear weight without pain at the fracture site) between the groups. Furthermore, the authors found no treatment effects of romosozumab on the incidence of unplanned revision surgery, physical function scores, or adverse events. The study concluded that romosozumab did not promote the healing of tibial fractures in this patient population.

Schemitsch *et al*[50] reported on a trial of romosozumab for the treatment of hip fractures in 332 patients (median age, 78 years; range 55−94 years). Patients were randomized to groups receiving a placebo (*n* = 89) or romosozumab at three different doses (70 mg, 140 mg, and 210 mg). Patients received subcutaneous romosozumab injections on postoperative days 1, 2, 6, and 12, and the percentage of patients with radiographic evidence of healing ranged from 66.2% to 78.6% at week 24 and from 89.1% to 93.2% at week 52, with no significant difference between the treatment groups. In addition, no significant difference occurred in the estimated median time to radiographic evidence of healing neither between the groups nor in functional mobility assessment, radiographic fracture healing assessment, and hip pain scores. Similar to the results with patients with tibial fractures, romosozumab did not improve fracture healing in patients with hip fractures.

It is unclear why bone healing was not accelerated in humans. In both studies, romosozumab was administered starting on postoperative day 1. Since romosozumab promotes the differentiation of osteoblasts from osteoprogenitors with little increase in osteoprogenitors[24], it is possible that administering romosozumab early in the fracture healing process period is not ideally timed. Yukata *et al*[51] reported that *SOST* gene expression were more abundant in the hard callus in the later stages of bone repair than in the soft callus in the early stages in a mouse tibia fracture model, and PTH administration upregulated *SOST* expression as the hard callus increased. These suggest the need to change the starting point of administration and to consider the combination of romosozumab and PTH, which has the effect of increasing immature cells. Additionally, in both studies the patients were treated at sites for high surgical standards of care and they received rigid fixation. The quality of the surgery and care may out-weighed the effects of romosozumab on fracture healing[49,50]. Future studies may focus on healing of serious fractures, which could only accomplish relatively un-rigid fixation.

**CONCLUSION**

Despite the preclinical success of Scl-Ab in promoting fracture healing in animals, currently, no clinical evidence exists for the positive effects of Scl-Ab for bone healing in humans. As an osteogenic agent in osteoporosis, Scl-Ab offers promising effects supported by reliable evidence. Although the drug targets the same bone tissue, further research is needed on the differences in the pathogenesis of osteoporosis and fracture, spatio-temporal expression pattern of *SOST* according to bone healing process, and corresponding timing and interval of drug administration.

**REFERENCES**

1 **Langdahl BL**, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, Goemaere S, Hyldstrup L, Jodar-Gimeno E, Keaveny TM, Kendler D, Lakatos P, Maddox J, Malouf J, Massari FE, Molina JF, Ulla MR, Grauer A. Romosozumab (sclerostin monoclonal antibody) versusteriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet* 2017; **390**: 1585-1594 [PMID: 28755782 DOI: 10.1016/S0140-6736(17)31613-6]

2 **Baron R**, Gori F. Targeting WNT signaling in the treatment of osteoporosis. *Curr Opin Pharmacol* 2018; **40**: 134-141 [PMID: 29753194 DOI: 10.1016/j.coph.2018.04.011]

3 **Lindsay R**, Zhou H, Cosman F, Nieves J, Dempster DW, Hodsman AB. Effects of a one-month treatment with PTH(1-34) on bone formation on cancellous, endocortical, and periosteal surfaces of the human ilium. *J Bone Miner Res* 2007; **22**: 495-502 [PMID: 17227219 DOI: 10.1359/jbmr.070104]

4 **Canalis E**. Wnt signalling in osteoporosis: mechanisms and novel therapeutic approaches. *Nat Rev Endocrinol* 2013; **9**: 575-583 [PMID: 23938284 DOI: 10.1038/nrendo.2013.154]

5 **Baron R**, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. *Nat Med* 2013; **19**: 179-192 [PMID: 23389618 DOI: 10.1038/nm.3074]

6 **Delgado-Calle J**, Sato AY, Bellido T. Role and mechanism of action of sclerostin in bone. *Bone* 2017; **96**: 29-37 [PMID: 27742498 DOI: 10.1016/j.bone.2016.10.007]

7 **Lim SY**, Bolster MB. Profile of romosozumab and its potential in the management of osteoporosis. *Drug Des Devel Ther* 2017; **11**: 1221-1231 [PMID: 28458516 DOI: 10.2147/DDDT.S127568]

8 **Gori F**, Lerner U, Ohlsson C, Baron R. A new WNT on the bone: WNT16, cortical bone thickness, porosity and fractures. *Bonekey Rep* 2015; **4**: 669 [PMID: 25987984 DOI: 10.1038/bonekey.2015.36]

9 **Poole KE**, van Bezooijen RL, Loveridge N, Hamersma H, Papapoulos SE, Löwik CW, Reeve J. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. *FASEB J* 2005; **19**: 1842-1844 [PMID: 16123173 DOI: 10.1096/fj.05-4221fje]

10 **Li X**, Zhang Y, Kang H, Liu W, Liu P, Zhang J, Harris SE, Wu D. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. *J Biol Chem* 2005; **280**: 19883-19887 [PMID: 15778503 DOI: 10.1074/jbc.M413274200]

11 **Leupin O**, Piters E, Halleux C, Hu S, Kramer I, Morvan F, Bouwmeester T, Schirle M, Bueno-Lozano M, Fuentes FJ, Itin PH, Boudin E, de Freitas F, Jennes K, Brannetti B, Charara N, Ebersbach H, Geisse S, Lu CX, Bauer A, Van Hul W, Kneissel M. Bone overgrowth-associated mutations in the LRP4 gene impair sclerostin facilitator function. *J Biol Chem* 2011; **286**: 19489-19500 [PMID: 21471202 DOI: 10.1074/jbc.M110.190330]

12 **Truswell AS**. Osteopetrosis with syndactyly; a morphological variant of Albers-Schönberg's disease. *J Bone Joint Surg Br* 1958; **40-B**: 209-218 [PMID: 13539104]

13 **Van Buchem FS**, Hadders HN, Ubbens R. An uncommon familial systemic disease of the skeleton: hyperostosis corticalis generalisata familiaris. *Acta radiol* 1955; **44**: 109-120 [PMID: 13258333]

14 **Brunkow ME**, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, Proll S, Skonier JE, Zhao L, Sabo PJ, Fu Y, Alisch RS, Gillett L, Colbert T, Tacconi P, Galas D, Hamersma H, Beighton P, Mulligan J. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet* 2001; **68**: 577-589 [PMID: 11179006 DOI: 10.1086/318811]

15 **Wergedal JE**, Veskovic K, Hellan M, Nyght C, Balemans W, Libanati C, Vanhoenacker FM, Tan J, Baylink DJ, Van Hul W. Patients with Van Buchem disease, an osteosclerotic genetic disease, have elevated bone formation markers, higher bone density, and greater derived polar moment of inertia than normal. *J Clin Endocrinol Metab* 2003; **88**: 5778-5783 [PMID: 14671168 DOI: 10.1210/jc.2003-030201]

16 **van Lierop AH**, Hamdy NA, van Egmond ME, Bakker E, Dikkers FG, Papapoulos SE. Van Buchem disease: clinical, biochemical, and densitometric features of patients and disease carriers. *J Bone Miner Res* 2013; **28**: 848-854 [PMID: 23074140 DOI: 10.1002/jbmr.1794]

17 **Balemans W**, Ebeling M, Patel N, Van Hul E, Olson P, Dioszegi M, Lacza C, Wuyts W, Van Den Ende J, Willems P, Paes-Alves AF, Hill S, Bueno M, Ramos FJ, Tacconi P, Dikkers FG, Stratakis C, Lindpaintner K, Vickery B, Foernzler D, Van Hul W. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet* 2001; **10**: 537-543 [PMID: 11181578 DOI: 10.1093/hmg/10.5.537]

18 **Li X**, Ominsky MS, Niu QT, Sun N, Daugherty B, D'Agostin D, Kurahara C, Gao Y, Cao J, Gong J, Asuncion F, Barrero M, Warmington K, Dwyer D, Stolina M, Morony S, Sarosi I, Kostenuik PJ, Lacey DL, Simonet WS, Ke HZ, Paszty C. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. *J Bone Miner Res* 2008; **23**: 860-869 [PMID: 18269310 DOI: 10.1359/jbmr.080216]

19 **McClung MR**. Emerging Therapies for Osteoporosis. *Endocrinol Metab (Seoul)* 2015; **30**: 429-435 [PMID: 26354487 DOI: 10.3803/EnM.2015.30.4.429]

20 **Tu X**, Rhee Y, Condon KW, Bivi N, Allen MR, Dwyer D, Stolina M, Turner CH, Robling AG, Plotkin LI, Bellido T. Sost downregulation and local Wnt signaling are required for the osteogenic response to mechanical loading. *Bone* 2012; **50**: 209-217 [PMID: 22075208 DOI: 10.1016/j.bone.2011.10.025]

21 **Rhee Y**, Allen MR, Condon K, Lezcano V, Ronda AC, Galli C, Olivos N, Passeri G, O'Brien CA, Bivi N, Plotkin LI, Bellido T. PTH receptor signaling in osteocytes governs periosteal bone formation and intracortical remodeling. *J Bone Miner Res* 2011; **26**: 1035-1046 [PMID: 21140374 DOI: 10.1002/jbmr.304]

22 **Kramer I**, Loots GG, Studer A, Keller H, Kneissel M. Parathyroid hormone (PTH)-induced bone gain is blunted in SOST overexpressing and deficient mice. *J Bone Miner Res* 2010; **25**: 178-189 [PMID: 19594304 DOI: 10.1359/jbmr.090730]

23 **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; **24**: 578-588 [PMID: 19049336 DOI: 10.1359/jbmr.081206]

24 **Ominsky MS**, Brown DL, Van G, Cordover D, Pacheco E, Frazier E, Cherepow L, Higgins-Garn M, Aguirre JI, Wronski TJ, Stolina M, Zhou L, Pyrah I, Boyce RW. Differential temporal effects of sclerostin antibody and parathyroid hormone on cancellous and cortical bone and quantitative differences in effects on the osteoblast lineage in young intact rats. *Bone* 2015; **81**: 380-391 [PMID: 26261096 DOI: 10.1016/j.bone.2015.08.007]

25 **Ominsky MS**, Vlasseros F, Jolette J, Smith SY, Stouch B, Doellgast G, Gong J, Gao Y, Cao J, Graham K, Tipton B, Cai J, Deshpande R, Zhou L, Hale MD, Lightwood DJ, Henry AJ, Popplewell AG, Moore AR, Robinson MK, Lacey DL, Simonet WS, Paszty C. Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. *J Bone Miner Res* 2010; **25**: 948-959 [PMID: 20200929 DOI: 10.1002/jbmr.14]

26 **Cosman F**, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CA, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C, Grauer A. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2016; **375**: 1532-1543 [PMID: 27641143 DOI: 10.1056/NEJMoa1607948]

27 **Saag KG**, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *N Engl J Med* 2017; **377**: 1417-1427 [PMID: 28892457 DOI: 10.1056/NEJMoa1708322]

28 **Schupbach D**, Comeau-Gauthier M, Harvey E, Merle G. Wnt modulation in bone healing. *Bone* 2020; **138**: 115491 [PMID: 32569871 DOI: 10.1016/j.bone.2020.115491]

29 **Zhong N**, Gersch RP, Hadjiargyrou M. Wnt signaling activation during bone regeneration and the role of Dishevelled in chondrocyte proliferation and differentiation. *Bone* 2006; **39**: 5-16 [PMID: 16459154 DOI: 10.1016/j.bone.2005.12.008]

30 **Hadjiargyrou M**, Lombardo F, Zhao S, Ahrens W, Joo J, Ahn H, Jurman M, White DW, Rubin CT. Transcriptional profiling of bone regeneration. Insight into the molecular complexity of wound repair. *J Biol Chem* 2002; **277**: 30177-30182 [PMID: 12055193 DOI: 10.1074/jbc.M203171200]

31 **Macsai CE**, Georgiou KR, Foster BK, Zannettino AC, Xian CJ. Microarray expression analysis of genes and pathways involved in growth plate cartilage injury responses and bony repair. *Bone* 2012; **50**: 1081-1091 [PMID: 22387305 DOI: 10.1016/j.bone.2012.02.013]

32 **Wise JK**, Sena K, Vranizan K, Pollock JF, Healy KE, Hughes WF, Sumner DR, Virdi AS. Temporal gene expression profiling during rat femoral marrow ablation-induced intramembranous bone regeneration. *PLoS One* 2010; **5** [PMID: 20957030 DOI: 10.1371/journal.pone.0012987]

33 **Marsell R**, Einhorn TA. The biology of fracture healing. *Injury* 2011; **42**: 551-555 [PMID: 21489527 DOI: 10.1016/j.injury.2011.03.031]

34 **Liedert A**, Röntgen V, Schinke T, Benisch P, Ebert R, Jakob F, Klein-Hitpass L, Lennerz JK, Amling M, Ignatius A. Osteoblast-specific Krm2 overexpression and Lrp5 deficiency have different effects on fracture healing in mice. *PLoS One* 2014; **9**: e103250 [PMID: 25061805 DOI: 10.1371/journal.pone.0103250]

35 **Montjovent MO**, Siegrist M, Klenke F, Wetterwald A, Dolder S, Hofstetter W. Expression of antagonists of WNT and BMP signaling after non-rigid fixation of osteotomies. *Bone* 2013; **53**: 79-86 [PMID: 23207801 DOI: 10.1016/j.bone.2012.11.027]

36 **Alzahrani MM**, Rauch F, Hamdy RC. Does Sclerostin Depletion Stimulate Fracture Healing in a Mouse Model? *Clin Orthop Relat Res* 2016; **474**: 1294-1302 [PMID: 26608966 DOI: 10.1007/s11999-015-4640-z]

37 **Ominsky MS**, Li C, Li X, Tan HL, Lee E, Barrero M, Asuncion FJ, Dwyer D, Han CY, Vlasseros F, Samadfam R, Jolette J, Smith SY, Stolina M, Lacey DL, Simonet WS, Paszty C, Li G, Ke HZ. Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone density and strength of nonfractured bones. *J Bone Miner Res* 2011; **26**: 1012-1021 [PMID: 21542004 DOI: 10.1002/jbmr.307]

38 **Liu Y**, Rui Y, Cheng TY, Huang S, Xu L, Meng F, Lee WY, Zhang T, Li N, Li C, Ke H, Li G. Effects of Sclerostin Antibody on the Healing of Femoral Fractures in Ovariectomised Rats. *Calcif Tissue Int* 2016; **98**: 263-274 [PMID: 26603303 DOI: 10.1007/s00223-015-0085-3]

39 **Suen PK**, He YX, Chow DH, Huang L, Li C, Ke HZ, Ominsky MS, Qin L. Sclerostin monoclonal antibody enhanced bone fracture healing in an open osteotomy model in rats. *J Orthop Res* 2014; **32**: 997-1005 [PMID: 24782158 DOI: 10.1002/jor.22636]

40 **Virdi AS**, Liu M, Sena K, Maletich J, McNulty M, Ke HZ, Sumner DR. Sclerostin antibody increases bone volume and enhances implant fixation in a rat model. *J Bone Joint Surg Am* 2012; **94**: 1670-1680 [PMID: 22992878 DOI: 10.2106/JBJS.K.00344]

41 **Yee CS**, Xie L, Hatsell S, Hum N, Murugesh D, Economides AN, Loots GG, Collette NM. Sclerostin antibody treatment improves fracture outcomes in a Type I diabetic mouse model. *Bone* 2016; **82**: 122-134 [PMID: 25952969 DOI: 10.1016/j.bone.2015.04.048]

42 **Feng G**, Chang-Qing Z, Yi-Min C, Xiao-Lin L. Systemic administration of sclerostin monoclonal antibody accelerates fracture healing in the femoral osteotomy model of young rats. *Int Immunopharmacol* 2015; **24**: 7-13 [PMID: 25479724 DOI: 10.1016/j.intimp.2014.11.010]

43 **Agholme F**, Li X, Isaksson H, Ke HZ, Aspenberg P. Sclerostin antibody treatment enhances metaphyseal bone healing in rats. *J Bone Miner Res* 2010; **25**: 2412-2418 [PMID: 20499342 DOI: 10.1002/jbmr.135]

44 **Agholme F**, Macias B, Hamang M, Lucchesi J, Adrian MD, Kuhstoss S, Harvey A, Sato M, Aspenberg P. Efficacy of a sclerostin antibody compared to a low dose of PTH on metaphyseal bone healing. *J Orthop Res* 2014; **32**: 471-476 [PMID: 24243768 DOI: 10.1002/jor.22525]

45 **McDonald MM**, Morse A, Birke O, Yu NYC, Mikulec K, Peacock L, Schindeler A, Liu M, Ke HZ, Little DG. Sclerostin antibody enhances bone formation in a rat model of distraction osteogenesis. *J Orthop Res* 2018; **36**: 1106-1113 [PMID: 28884841 DOI: 10.1002/jor.23726]

46 **Virk MS**, Alaee F, Tang H, Ominsky MS, Ke HZ, Lieberman JR. Systemic administration of sclerostin antibody enhances bone repair in a critical-sized femoral defect in a rat model. *J Bone Joint Surg Am* 2013; **95**: 694-701 [PMID: 23595067 DOI: 10.2106/JBJS.L.00285]

47 **Tinsley BA**, Dukas A, Pensak MJ, Adams DJ, Tang AH, Ominsky MS, Ke HZ, Lieberman JR. Systemic Administration of Sclerostin Antibody Enhances Bone Morphogenetic Protein-Induced Femoral Defect Repair in a Rat Model. *J Bone Joint Surg Am* 2015; **97**: 1852-1859 [PMID: 26582615 DOI: 10.2106/JBJS.O.00171]

48 **Kruck B**, Zimmermann EA, Damerow S, Figge C, Julien C, Wulsten D, Thiele T, Martin M, Hamdy R, Reumann MK, Duda GN, Checa S, Willie BM. Sclerostin Neutralizing Antibody Treatment Enhances Bone Formation but Does Not Rescue Mechanically Induced Delayed Healing. *J Bone Miner Res* 2018; **33**: 1686-1697 [PMID: 29694687 DOI: 10.1002/jbmr.3454]

49 **Bhandari M**, Schemitsch EH, Karachalios T, Sancheti P, Poolman RW, Caminis J, Daizadeh N, Dent-Acosta RE, Egbuna O, Chines A, Miclau T. Romosozumab in Skeletally Mature Adults with a Fresh Unilateral Tibial Diaphyseal Fracture: A Randomized Phase-2 Study. *J Bone Joint Surg Am* 2020; **102**: 1416-1426 [PMID: 32358413 DOI: 10.2106/JBJS.19.01008]

50 **Schemitsch EH**, Miclau T, Karachalios T, Nowak LL, Sancheti P, Poolman RW, Caminis J, Daizadeh N, Dent-Acosta RE, Egbuna O, Chines A, Maddox J, Grauer A, Bhandari M. A Randomized, Placebo-Controlled Study of Romosozumab for the Treatment of Hip Fractures. *J Bone Joint Surg Am* 2020; **102**: 693-702 [PMID: 31977817 DOI: 10.2106/JBJS.19.00790]

51 **Yukata K**, Xie C, Li TF, Takahata M, Hoak D, Kondabolu S, Zhang X, Awad HA, Schwarz EM, Beck CA, Jonason JH, O'Keefe RJ. Aging periosteal progenitor cells have reduced regenerative responsiveness to bone injury and to the anabolic actions of PTH 1-34 treatment. *Bone* 2014; **62**: 79-89 [PMID: 24530870 DOI: 10.1016/j.bone.2014.02.002]

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**Table 1 The efficacy of sclerostin antibody for bone healing has been demonstrated in several reports with animal models**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Animal model** | **Bone** | **Bone injury model** | **Dosage, frequency** | **Major findings** | **Ref.** |
| Mouse | Tibia | Osteotomy | 100 mg/kg, 1/wk | BV/TV↑, strength↑ | [36] |
| Rat | Femur | Fracture | 25 mg/kg, 2/wk | Callus↑, BMC↑, BV/TV↑, strength↑ | [37] |
| Cynomolgus monkey | Fibula | Osteotomy | 30 mg/kg, 1/2 wk | Callus↑, BMC↑, strength↑ | [37] |
| Rat | Femur | Ablation | 25 mg/kg, 2/wk | Fixation strength↑, cortical thickness↑, BV/TV↑ | [40] |
| Rat | Femur | Fracture | 25 mg/kg, 2/wk | BMD↑, BV/TV↑, strength↑, MS/BS↑, BFR/BS↑ | [38] |
| Rat | Femur | Osteotomy | 25 mg/kg, 2/wk | Callus↑, BMD↑, BV/TV↑, strength↑, bone area↑, cartilage↓ | [39] |
| Mouse | Femur | Fracture | 25 mg/kg, 2/wk | BV/TV↑, BMC↑ | [41] |
| T1DM  mouse | Femur | Fracture | 25 mg/kg, 2/wk | BV/TV↑, BMC↑ | [41] |
| Rat | Femur | Osteotomy | 25 mg/kg, 2/wk | Mature callus↑, BMC↑, BMD↑, strength↑ | [42] |
| Rat | Tibia | Metaphyseal  screw | 25 mg/kg, 2/wk | Pull-out strength↑, bone volume surrounding screw↑ | [43] |
| Rat | Femur | Distraction osteogenesis | 25 mg/kg, 2/wk | Union rate→, (united bones) strength↑, bone volume↑ | [45] |
| Rat | Femur | Critical defect | 25 mg/kg, 2/wk | Union rate↑, bone formation markers↑ | [46] |
| Mouse | Femur | Osteotomy rigid fix | 25 mg/kg, 2/wk | Periosteal and/or intracortical bridging→, endosteal bridging↑ | [48] |
| Mouse | Femur | Osteotomy semi-rigid fix | 25 mg/kg, 2/wk | Periosteal and/or intracortical bridging→, endosteal bridging↑ | [48] |

T1DM: Type 1 diabetes mellitus; BV/TV: Bone volume to total bone volume ratio; BMC: Bone mineral content; BMD: Bone mineral density; MS/BS: Mineralizing surface rate; BFR/BS: Bone formation rate.

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