

Dear editor,

World Journal of Orthopedics

Manuscript # 64688

We thank you and the reviewer for the very useful comments and your critical and careful review of our manuscript. To better understand the effect of sclerostin antibody in bone healing, we added one table, which includes the animal data.

We have responded in a point-by-point fashion to the comments from the Reviewer and indicated how the suggestions have been incorporated in the revised manuscript where appropriate. We have used red colored font in the revised manuscript for easy identification. We believe the manuscript has been significantly improved and hope that it is suitable for publication in **World Journal of Orthopedics**.

We look forward to hearing from you at your earliest convenience.

Reviewer #1

Specific Comments to Authors: In this paper the effect of sclerostin antibody on bone healing is analysed. Besides a robust literature on osteoporosis, only two papers are available on this topic in humans and the results of these two studies do not support the use of romosozumab to accelerate bone healing. Consequently, in this 10-page paper, just one page is sufficient to analyse the specific topic: in my opinion the amount of available data are inappropriate for a review. Accordingly, the specific topic of the paper could be a paragraph of a more general review on the effect of romosozumab on osteoporosis, which I suggest to prepare.

Response: Thank you for your good suggestion. You are right. As you mentioned, clinically available information on romosozumab for bone fractures is limited. Therefore, we wanted to summarize the current

information and mention some future issues. Also, to better understand the effects of Scl-Ab in bone healing, we summarized the animal data in Table.

Reviewer #2:

Specific Comments to Authors: This manuscript focuses on the effects of the sclerostin antibody on bone healing. This paper presented that Scl-Ab stimulates bone formation via canonical wnt- β -catenin pathway, and then discussed the current experimental and clinical evidence of Scl-Ab in bone healing. Then it presented that Scl-Ab has shown positive effects on bone healing in several animal models, whereas in two clinical studies, Scl-Ab failed to show positive effects in the femur and tibia. Overall the study presents that the effect of Scl-Ab on osteoporosis and fractures are different. In the future, research is required to better understand the timing and localization of the appearance of sclerostin-expressing cells according to this pathogenesis, as well as to identify the timing and intervals of drug administration.

Comment: 1.The abstract did not summarize and reflect the work described in the manuscript and it should be organized better.

Response: Thank you for your good suggestion. As the reviewer mentioned, the abstract did not summarize the work. We have summarized the content as much as possible.

2.As to the mechanisms of action, some researches have showed that low density lipoprotein receptor-related protein 4 (LRP4) can also associate with sclerostin, which enhances the suppressive effect of sclerostin on Wnt signaling[1]. The author need to pull this information together in the context. (Line 111-122) Reference 1. Leupin Olivier,Piters Elke,Halleux Christine et al. Bone overgrowth-associated mutations in the LRP4 gene impair sclerostin facilitator function.[J] .J Biol Chem, 2011, 286: 19489-500.

Response: Thank you very much. We added the reference in the manuscript. Line 104-106 and reference #11.

3. There were some inconsistencies in this paragraph as listed below. In addition, the author needs to add a few sentences, which would make it easy to understand the difference between Scl-Ab and PTH in this paragraph. Line 172: The osteoprogenitors increased to similar levels in both groups at week 4. Line 177: These results suggest that Scl-Ab increases the differentiation induction of osteoprogenitors to osteoblasts only, while PTH1-34 increases both the differentiation induction of osteoprogenitors to osteoblasts and the number of osteoprogenitors, although the level of bone formation was similar or even higher in Scl-Ab than in PTH1-34.

Response: Thank you for your good suggestion. We added the following sentences in Line 155-162.

"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.

Reviewer #3:

Specific Comments to Authors: Authors could discuss why Scl-Ab apparently worked well in animal models of fracture healing and not in clinical cases.

Response: Thank you for your encouragement.