Reviewer's report

Title: Triweekly Administration of Parathyroid Hormone (1-34) Accelerates Bone Healing in a Rat Refractory Fracture Model

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Reviewer: Aaron Schindeler

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PTH(1-34) is a potent bone anabolic that has previously been used in multiple models of bone healing. While this has been successful in some models, it is less applicable in others (e.g. Tagil et al 2010). Similarly teriparitide has had clinical utility in some fracture situations but improved fracture repair is not an approved indication. In this study authors use a rat model (femoral fracture with cautery) that leads to non-union and treat with 100ug/kg 3 times per week for 8 weeks. Other studies have investigated weekly PTH and found it surprisingly effective, although the dose of 100ug/kg is quite high. There doesn't appear to be anything particularly original with the author's approach or analysis.

Overall the study is poorly written with insufficient citation being the main problem. In addition the outcomes are very amateurish, and it is suggested the authors look at a Journal of Orthopaedic Research or Bone paper to look at the quality of radiography, microCT, histology, and biomechanical testing that is published in these journals.

Comments:

1. The introduction is insufficient without adequate description of models where PTH is less effective and failed clinical studies. In addition, discussion of other papers justifying the dosing regimen are required. I recently read a paper where they cited once-weekly PTH use in monkeys and other animals, and described daily, twice weekly, and thrice weekly PTH dosing by comparison. This sort of material needs to be included.

2. The methods for fracture repair as a modified RUST score should be properly cited.
3. The histology, like all of the measures is very simple and there is no attempts at quantification or any measures such as osteoclast or osteoblast staining. Or staining for residual cartilage.

4. As a note, 4 point bending is superior to 3 point bending for fractures as there are less issues with plastic deformation at the fracture site as well 3 point bending forces a break at the fracture when adjacent to the callus can be the weakest point. For biomechanical tests, were only united fractures tested? How do you test non-unions (or are they given a 0 value) and is this a relevant outcome? This would presumably lead to a highly bimodal distribution.

5. For radiographic assessment a Fisher's exact test may be superior to a chi-squared test, although both are technically acceptable.

6. Graphs should ideally be presented as dot-plots so that all individual data points can be seen. This is particularly the case for mechanical tests, which can be highly variable (e.g. failure energy).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.
Yes

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I have received research support from Celgene, N8 Medical, and Novartis.
I have received speaking fees from Amgen.
I have no financial competing interests to declare related to PTH(1-34) research.

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