Reviewer's report

Title: Alterations in Osteoclast Function and Phenotype Induced by Different Inhibitors of Bone Resorption - Implications for Osteoclast Quality

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Reviewer: Elizabeth Bradley

Reviewer's report:

In the article titled “Alteration in Osteoclast Function and Phenotype Induced by Different Inhibitors of Bone Resorption—Implications for Osteoclast Quality”, the authors sought to determine if inhibition of osteoclast acid secretion or protease activity result differences in the ability of osteoclasts to resorb the organic and inorganic matrices, therefore differentially affecting bone quality. The enclosed data support the authors’ conclusion that inhibitors targeting acid secretion and protease activity have difference effects on bone resorption, with acidification inhibitors significantly decreasing both the organic and inorganic resorption. In contrast, the authors also claim that protease inhibition decreased organic resorption, without dramatically affecting inorganic resorption. However, there are a number of changes and additional experiments which would further support the authors’ claims. These suggestions are listed below in a point-by-point review:

1. Minor Essential Revision:
   a. The text labels in figure 2A are very difficult to read. Perhaps these labels indicating the type of inhibitor could be placed to the side of each panel in figure 2A in black text.

2. Major Compulsory Revision While the decrease in resorption pit number with acidification inhibitors is expected, the increase in pit formation observed with E64 treatment alone is surprising. The authors should determine if an increase in cell number, motility or survival can account with E64 treatment occurs which would account for the increase in pit counts.

3. Major Compulsory Revision: The increase in the MMP zymograph with E64 treatment is apparent, but may not be significant. Furthermore, treatments with GM and the combination of E64 and GM may also be increasing MMP, which was not observed in figure 4A. The authors should quantitate each band in the zymograph and display the results±error.

4. Major Compulsory Revision: Throughout the manuscript the authors asses cell viability using a colormetric assay and no significant changes in cell viability are noted, except with doses of 30uM and higher of Iban. This is fine, except that the authors are proposing that the lower concentrations of Iban also induce cell death, but that this effects is masked by the presence of mononuclear cells. The authors should therefore determine if Iban in deed does target osteoclast specific cell death while no affecting mononuclear cell viability.
This manuscript warrants publication given the above mentioned corrections and additional data are incorporated. Thus, I suggest that this manuscript be accepted following revision.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.