Author's response to reviews

**Title:** Myoblast sensitivity and fibroblast insensitivity to osteogenic conversion by BMP-2 correlates with the expression of Bmpr-1a

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**Author's response to reviews:** see over
The Editor,
BMC Musculoskeletal Disorders,

3rd April, 2009

To the Editor,

Thank you for getting back to us with a request to revise and resubmit our paper “Myoblast sensitivity and fibroblast insensitivity to osteogenic conversion by BMP-2 correlates with the expression of Bmpr-1a.”

We are submitting a revised version of Figure 4.

Reviewer 3 had no further changes. Reviewer 1 requested a change to graph format in Figure 4, which we have made to make it more consistent with other graphs. We have attempted again to address the comments by Reviewer 2 in our schedule of changes. However, we must say that his comments are not entirely clear, and this may be why the reviewer found our responses unsatisfactory.

We sincerely hope that this manuscript can now be approved at an editorial level, particularly considering the positive assessments by the other reviewers.

Yours sincerely,

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Schedule of Changes

Reviewer 1:
Major Revisions: None
Minor Revision:
1. Change Figure 4 to straight line graph for consistency.
This change has been made.

Reviewer 2:
1. C2C12 are myoblasts. NIH/3T3 are fibroblasts. MC3T3E1 are osteoblasts. I cannot understand why the authors used bone marrow cells. If they need immature cells, they should use younger mice.

After our original submission, we were asked by this reviewer to explain the use of bone marrow cells as opposed to calvaria-derived cells. Our response in our first revision was to stress that the use of bone marrow cells was a deliberate one because it was found with myogenic cells and fibroblasts in an orthopaedic injury. Calvarial cells on the other hand are not present. To reiterate, the purpose of the study is to model the response of cell types present at the site of skeletal repair to osteogenic stimulation by BMPs. We believe that the cell types used are suitable for this.

In addition, we maintain there is a clear difference between animal maturity and cellular maturity – young animals can have fully differentiated cells and there is ample evidence that progenitor/stem cells are present in mature animals. A cell would not be considered immature just because it was sourced from a young animal.

2. In vitro and ex vivo studies are totally different. The authors do not seem to improve this point. It is necessary to describe the results of ex vivo study using these treated cells.

In our original response, we were unsure of this comment and asked for further clarification. We have now conferred with gene therapy specialist, who suggested that the reviewer may be referring to the implantation of treated cells into live mice. These experiments are not within the scope of this study, which is an in vitro assessment of cell potential. Moreover, such a study would be applicable for assessing cell contribution in a gene therapy context, but would not adequately gauge the contribution of endogenous, unmodified progenitors. To this end, we are undertaking completing studies focused on the in vivo cell tracking of endogenous myogenic progenitors to bone that will form the basis of a separate paper.