Reviewer's report

**Title:** Rapid cell culture and pre-clinical screening of a transforming growth factor-beta (TGF-beta) inhibitor for orthopaedics

**Version:** 1 **Date:** 8 February 2010

**Reviewer:** Martin Stoddart

**Reviewer's report:**

This article describes in vitro and in vivo investigations into the ALK selective inhibitor SB431542, in order to determine its effects into osteochondral differentiation. Unfortunately I do not feel it is ready for publication in its current form.

The article appears to have 2 main aims, one is the effect of SB431542, while a second more conceptual aim is the use of in vitro and in vivo models as a rapid pre-screen (as emphasised by the title and the concluding paragraph of the introduction). The second aim as correctly highlighted by the authors is an extremely important one as adequate preclinical models are currently lacking.

While the first aim is covered quite well, the authors have not raised a convincing argument for the second aim, and the reader is left to speculate which model should be used and why the models were not comparable as the authors do not put forward a hypothesis.

**Major Compulsory Revisions**

The discrepancy between the in vitro data and the in vivo data is not adequately covered in the discussion. There is no discussion of the ectopic pellet culture. One potential reason for the difference in results could be that the cell line does not act in a manner which would be expected from primary cells.

While cell lines are frequently used, it is becoming increasing apparent that for detailed molecular pathways the choice of line is critical. The authors should try repeating the studies with primary mouse MSCs or a different cell line to determine whether it’s a peculiar feature of the cells which has led to the differences.

In this study it becomes more pertinent as it has been demonstrated that the response of MC3T3-E1 cells to TGF# and BMP2 is dependant on passage number (see below). This would suggest that this line might not be the best choice for studies involving these factors. The authors of this study do not mention the passage number of the cells used.

**Effect of serial passage on gene expression in MC3T3-E1 preosteoblastic cells: a microarray study.**

Huang W, Carlsen B, Rudkin GH, Shah N, Chung C, Ishida K, Yamaguchi DT,
Serial passage of MC3T3-E1 cells alters osteoblastic function and responsiveness to transforming growth factor-beta1 and bone morphogenetic protein-2.

Chung CY, Iida-Klein A, Wyatt LE, Rudkin GH, Ishida K, Yamaguchi DT, Miller TA.


**Level of interest:** An article whose findings are important to those with closely related research interests

**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