Reviewer's report

Title: Modelling NF1 tibial dysplasia and its treatment with lovastatin.

Version: 1 Date: 17 April 2008

Reviewer: David G Little

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This is an important study looking at bone healing in NF1. The field has recently realised that double inactivation of NF1 may be responsible for poor bone healing in congenital pseudarthrosis of the tibia and other bone disorders in NF1.

This group has created Prx-Cre x NF1 flox mice in which there is double inactivation of NF1 in the libs. The phenotype showed tibial bowing but not fractures. This experiment models bone repair with a drill hole through the proximal tibia in WT and affected mice, and looks at the response to lovastatin treatment.

Important findings are

Abnormal healing in Prx-Cre NF1 flox mice, with increases in fibrous and cartilagenous tissue and decreased BV/TV.

Improved responses when statins were given based on histology and histomorphometry

Correction of Ras signalling with statin treatment (see comment and concern below)

Although this is primarily a descriptive paper, it is the first study to examine statins for NF1 in bone repair so it is of great relevance. The scope and impact certainly warrants its publication.

There are a few issues with writing and experimental design that should be addressed before acceptance-

Major compulsory revisions:

1. Group sizes are a bit confusing - one can infer total mice = 24 and group size n=6 was used from the abstract and paragraph 2 of the results. Group sizes should be put in the methods. Seeing as decalcified and resin histology were done, were groups split n=3 and n=3 for histology? Were all n=6 used for uCT outcomes? What happened to the data from the 4th group (i.e. lovastatin treated controls)? A table or some delineation of numbers is required.

2. The Ras signalling work was done in calvarial lysates where the Prx-Cre should not be expressed. The Nf1 -/- cells should only be in the limbs. Thus the cells from calvaria should be Nf1+/+? This would mean there should be no differences in Erk. Marrow cells taken from the limbs or bones of the limbs would surely be better to look at this signalling?
Minor Essential Revisions:
1. The results section is written in present tense rather than past tense.
2. More methods detail should be given, particularly for preparation of lovastatin (still in brief), and calvarial lysate preparation (is this bone, bone cells...)
3. Figures should be in the order referred to in the text (1,2,3... not 1,2,5...)
4. Clarify that these are representative sections and of how many animals?

Discretionary Revisions:
It may be helpful to switch Fig 1 and Fig 2 around (show decalcified histology first).

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of outstanding merit and interest in its field

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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’