Author's response to reviews

Title: In-vivo generation of bone via endochondral ossification by in-vitro chondrogenic priming of adult human and rat mesenchymal stem cells

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Author's response to reviews:

Dear Ms Gorton

Please find attached the revised manuscript containing statements of conflicts of interest and author contributions. Original cover letter is also provided below.

Kind Regards

Eric Farrell

Dear Editor

Please find attached a manuscript entitled In-vivo generation of bone via endochondral ossification by in-vitro chondrogenic priming of adult human and rat mesenchymal stem cells. In this article we describe a novel means of bone tissue engineering via the mechanism of endochondral ossification instead of the usual route of intramambranous ossification. To date, tissue engineering approaches to bone formation and repair by direct osteogenic differentiation (intramambranous ossification) of mesenchymal stem cells have been quite unsuccessful with core necrosis being one of the major hurdles to overcome as a result of lack of blood supply to the construct upon implantation. Previously we hypothesised that this might be overcome by inducing the alternative natural route of bone formation (endochondral ossification) in MSCs by chondrogenic differentiation in vitro. We feel that this article significantly contributes to a small but growing body of evidence by confirming bone formation by endochondral
Ossification in adult human MSCs, but also in an immunocompetent rat model. We further assess the ability to optimise and understand this process by the use of two brief osteogenic stimuli in vitro to further progress differentiation prior to implantation for improved bone quality and quantity. Finally we examine the important issue of the role of host and donor cells in the process of new bone formation using transgenic animals expressing human placental alkaline phosphatase. This work represents an exciting step forward in the area of endochondral ossification for tissue engineering and regenerative medicine purposes and addresses critical questions in the understanding of this approach. We believe that this article will be of interest to many of your readers and being one of a small number of papers yet to be published in this area will also likely be cited frequently.

I look forward to hearing your decision in this matter

Kind Regards

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