Reviewer’s report

Title: Silencing Dkk1 Expression Rescues Dexamethasone-Induced Suppression of Primary Human Osteoblast Function

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Reviewer: John Shaughnessy

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The manuscript by Dr. Butler, et al reported that dexamethasone (Dex) attenuates human osteoblast differentiation and, concomitantly, inhibition of the canonical Wnt signaling pathway in these cells. Results associated with has Dex on b-catenin and TCF transcriptional activity have validated results from of previous studies that demonstrating that dex attenuates canonical Wnt signaling in human osteoblasts. The authors also provide evidence that investigate the biological role of Dkk1 as related to glucocorticoid-induced impaired osteoblast function in human primary osteoblast cells. Further validation of that biological role of interfering Dkk1 function in Dex-disturbed osteoblast function could further validated in the studies as described below as following, this study will would extend our knowledge of in Dex-induced osteopenia into human osteoblasts and provide the insight for targeting Dkk1 or increasing e Wnt signaling as a potential alternative strategies for treatment of the harmful effects of glucocorticoids.

1. Since the experiments design for determining the Dex on osteoblastic differentiation is different from standard methods (the exposure to Dex was too short to determine the ALP activity and RSA), the author should prolong the time for ALP at least 72 hours or longer or, for ARS, at least 2 or 3 weeks.

2. To support the conclusion in the study that interfering with Dkk1 expression rescues Dex-disturbed osteoblast function via impairment of Wnt-b-catenin signaling pathway, neutralizing anti-Dkk1 antibody should be utilized to validate the role of silencing Dkk1 as a means of reducing release DEX-induced osteogenic impairment.

3. Experiments should be done to confirm that silencing of Dkk1 has an effect on Wnt signaling (TCF transcriptional activity measured by luciferase report assay and b-catenin protein alteration).