

Dear editor,

Thank you very much for your decision letter and advice on our manuscript entitled “Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease.” We also thank the reviewers for their constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are highlighted in red font in the **67210-Supplementary-Material-revision** (This is a revised manuscript) . In addition, our point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by *Medjaden* Bioscience Limited.

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely.

## Replies to Reviewers

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

### Specific Comments

1. Pathophysiology of anemia in CKD includes many important factors some of which have not been mentioned by the authors, such as presence of comorbidities, resistance of bone marrow to EPO action due to uremic toxins, reduced red cell life span, hepcidin metabolism dysfunction (“Pathophysiology of renal anaemia”, Colin C Geddes)

**Response:** Thank you for your insightful suggestion. We have added the pathophysiological factors of anemia in CKD and added relevant literature to the citation list (Page 4, Lines 95-100).

2. Please add reference(s) for the sentence “According to prior research and experience from clinical practice, the pathogenesis and potentially the treatment of renal anemia and abnormal bone metabolism may share multiple similarities”.

**Response:** Thank you for your thoughtful suggestion. We have modified this sentence appropriately and added relevant literature to the citation list (Page 4, Line 107).

3. Please add reference for the sentence “VDR is also expressed by immunocytes, and VDR activation on these cells enhance their anti-inflammatory effects and also promote the proliferation of erythrocyte progenitor cells”.

**Response:** Thank you for your thoughtful suggestion. The articles cited in this sentence are References Nos. 18 and 19 (Page 5, Line 147).

4. In Figure 1, overproduction is associated with cytokine production during inflammation, but other factors are also involved like decreased renal clearance. Also use correctly CFU and CUF abbreviations as they seem to represent the same concept. .

**Response:** Thank you for your thoughtful suggestion. Regarding factors leading to the overproduction of hepcidin, we have made necessary supplements to the revised figure (67210-Figures.pptx), and also corrected the spelling error of the word CFU (Page 21, Lines 590).

5. The suppression of hepcidin and the resulting increased iron availability for erythropoiesis are mediated by erythroferrone (ERFE), in response to stimulation by erythropoietin. There is no discussion about the role of ERFE in anemia in CKD (Hanudel et al., “Levels of the erythropoietin-responsive hormone erythroferrone in mice and humans with chronic kidney disease”). .

**Response:** Thank you for your thoughtful suggestion. We have added discussion about the role of ERFE in anemia in CKD (Page 6, Lines 167-170). We have also added this to the revised Figure (67210-Figures.pptx).

## **Replies to Science editor and Company editor-in-chief**

Thanks to the editors for the opportunity to revise the manuscript.

### **Specific Comments**

Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (2) The “Author Contributions” section is missing. Please provide the author contributions; And (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

(1) We have provided original pictures, which were prepared and arranged using PowerPoint (67210-Figures.pptx).

(2) We have added the author contributions to the revised manuscript (Page 1, Lines 17-20);

(3) In all references, we have added the PMID and DOI numbers.

Finally, we further revised the manuscript according to the Guidelines and Requirements for Manuscript Revision.