

September 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4840-review.doc).

Title: Advances in homology directed genetic engineering of human pluripotent and adult stem cells

Authors: Kalpith Ramamoorthi, Donald Curtis, and Prashanth Asuri

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 4840

We appreciate the comments and suggestions of the reviewers, and have responded to them as outlined below.

Comment 1: The authors made attempt to describe recent approaches to modify genome of stem cells. However, the most modern technique, as the TALEN technology, is only shortly mentioned. Pages and Figures should be numbered.

In the current manuscript, we primarily focused on ZFNs because ZFNs have been much more widely studied and there are both for-profit and nonprofit organizations that distribute ZFNs for various human genome sequences. On the other hand, the discovery of TALENs is relatively recent and their use in editing human stem cell genome is less widely reported. However, keeping in mind the editor's comments, we have added a section to the revised manuscript that highlights a few examples of the application of TALEN technology to modify the human stem cell genome.

Page numbers and figure numbers have been added to the revised manuscript.

Comment 2: This is a very well written, informative review article. The references are chosen carefully and used appropriately. There is one potential point of improvement, however: I felt that the directed evolution figure (Figure 3) could be made more clear, especially in the screening step.

We thank the reviewer for his/her kind comments.

A fully detailed explanation of the various steps involved in the directed evolution of AAV is beyond the scope of this review and we have pointed the readers to other relevant AAV reviews. In addition, we have also additional information regarding the directed evolution process both to the main text and the figure legend of the revised manuscript.

Comment 3: This is an interesting and unusual review that certainly deserved publication. No specific comments. The authors should however check that all abbreviations have been correctly defined.

We thank the reviewer for his/her kind comments. We have confirmed that all the abbreviations have been defined appropriately.

Other comments: The first author should cite his/her own work on the subject, to be clear, that the review is written by the expert in the field.

We apologize for any confusion caused by this. The first and second authors of the paper - Kalpith Ramamoorthi and Donald Curtis are graduate student in Dr. Asuri's lab. Dr. Prashanth Asuri is the main author on the manuscript. Dr. Asuri worked at University of California, Berkeley for two years on gene editing of human pluripotent stem cells and the current manuscript cited two works published by Dr. Asuri on the use of evolved AAV and ZFNs to edit human stem cells (Ref. 36 and Ref. 37).

Thank you again for publishing our manuscript in the *World Journal of Stem Cells*.

Yours sincerely,

A handwritten signature in black ink, appearing to be 'Prashanth Asuri', with a long horizontal line extending to the right.

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