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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells
**ESPS manuscript NO:** 24267
**Title:** Characterization and genetic manipulation of primed stem cells into a functional naïve state with ESRRB
**Reviewer's code:** 02446280
**Reviewer's country:** Russia
**Science editor:** Jin-Xin Kong
**Date sent for review:** 2016-01-15 11:01
**Date reviewed:** 2016-01-18 17:42

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [Y] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [ ] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [Y] Minor revision |
| [ ] Grade E: Poor | | [Y] No | [ ] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

The paper "Reprogramming of non-functional stem cells into a functional state with ESRRB" by Rosello et al describes functional changes that took place in mouse ESC liens upon transduction with lentivaral constructs containing various genes including ESRRB. The paper is well written and addresses an important issue of the ESC functionality. Authors performed transcriptom analysis of functional and non-functional ESC lines and found some differences in gene expression signature. Overexpression of the downregulated ESRRB gene along with Klf5 and cMyc provided better chimera formation. The major drawback of the manuscript is the misleading use of the word reprogramming. Indeed, cells changed their functional properties however they did not change the overall program, they still have same phenotype and hopefully ES markers expression. Term reprogramming is often used to describe the process that changes cellular fate, i.e. from somatic to pluripotent, from fibroblasts to neurons. In this particular case ESCs do not change their fate instead they constitutively overexpressed few endogenous genes and their silencing were not observed. At least Authors did not mention it. Authors did not demonstrate whether overexpression of 3 genes

leads to the changes in the expression of other genes, what is the impact on cellular program. It means that cells were not reprogrammed but just forced to survive in the embryo by constitutive overexpression. I recommend to substitute wording "reprogramming" for "overexpression" throughout the manuscript including the title.

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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells
**ESPS manuscript NO:** 24267
**Title:** Characterization and genetic manipulation of primed stem cells into a functional naïve state with ESRRB
**Reviewer's code:** 00076088
**Reviewer's country:** Hungary
**Science editor:** Jin-Xin Kong
**Date sent for review:** 2016-01-15 11:01
**Date reviewed:** 2016-01-26 18:06

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [ ] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [Y] Grade C: Good | [Y] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [Y ] No | [Y] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y ] No | |

## COMMENTS TO AUTHORS

This paper reviews the key pluripotency gene expression profiles in mouse ES cells and suggests that ESRRB is a key factor in providing a "functional" ES phenotype. There are numerous problems with this paper: 1. The title and the concept of "functional" and "non-functional" ES cells is entirely inappropriate. Both of these cell types are pluripotent, that is they can differentiate into all types of tissues, and chimera formation is another potential, which e.g. cannot be tested in human ES cells. The current, acceptable terminology may be "naive" ES cells for those which can form chimeras and "primed" for those which may not (based on different origin, gene expression profile, etc.) 2. The expression of ESRRB may be lower in the primed cells but this is not visible in Figure 1. This Figure is not really appropriate to appreciate the differences (the colors are not separated in many cases). 3. ESRRB is clearly involved in the overexpression of Nanog, thus an appropriate control for "reprogramming" of primed cells should have included Nanog. In the absence of this experiment the exclusive role of ESRRB cannot be appreciated in naive state generation. 4. The are numerous problems in the language and details of the manuscript - e.g. the commonly used feeder mouse

embryonic fibroblast preparation is most detailed, while the generation of naive and primed mES cells is not described at all. The methods should be focused on the novelties suggested in the manuscript. 5. Table 3 and 4 should be provided in supplemental materials.

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# ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Stem Cells
**ESPS manuscript NO:** 24267
**Title:** Characterization and genetic manipulation of primed stem cells into a functional naïve state with ESRRB
**Reviewer's code:** 01047169
**Reviewer's country:** South Korea
**Science editor:** Jin-Xin Kong
**Date sent for review:** 2016-01-15 11:01
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| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|---|---|---|---|
| [ ] Grade A: Excellent | [ ] Grade A: Priority publishing | Google Search: | [ ] Accept |
| [ ] Grade B: Very good | [Y] Grade B: Minor language polishing | [ ] The same title | [ ] High priority for publication |
| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [Y ] No | [Y] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y ] No | |

## COMMENTS TO AUTHORS

This manuscript compares non-functional ES cells (which are defective in germ line transmission) and functional and reprogrammed ES cells in various respects. The morphology and expression of key molecules are similar, but expression of some genes were down-regulated or up-regulated in non-functional ES cells. By showing conversion of non-functional ES cells to functional ES cells by reprogramming, the authors suggested some genes like ESRRB can be used for enhanced efficiency in establishment of functional ES cells. They showed interesting facts and suggested a way to determine the state of obtained ES cells at early time point during the time-consuming process. However, there are some points to be clarified. 1. In Fig. 1, the authors showed only morphology of the ES cells. I recommend to show the AP staining results, too. 2. The Figure 2 is too complex and confusing. The authors described that the expression level of several genes in fibroblast was taken as 1 in the text (p13). However, in the figure the position of fibroblast (red box) is around 0.1. Please check it. 3. In Fig. 2, is expression of ERAS in functional ES cells higher than non-functional cells? I can't find green box there. 4. Is it possible to split Fig.2 somehow? For example, one figure shows only c-Myc, Nanog,

Oct4, and Sox2 in functional and non-functional cells first; another figure shows the genes (if you need them) and other genes differentially expressed in the two cells along with reprogrammed cell. In that way, it is much easier to read the paper and follow the results. In terms of order of the genes, I think it is easier to follow if you arrange the genes in the data according to the order that you explain in the text rather than just alphabetical order. You may put the down-regulated genes first (such as ATRX etc) and then show up-regulated genes (such as BMP7 and Pax6) later, it will be great. 5. In Table 3, Pax3 is marked as red but never commented. What is the function and meaning of the gene expression? 6. At the line 4 in page 14, "a positive log fold change indicates that gene expression is lower in the functional cells". Is it right? It seems to me reversed. 7. Please be consistent in naming the gene names, especially c-Myc. C-Myc, c-myc, C-myc ….. 8. There are many English errors such as typos and space. Please look over the manuscript carefully.