

Format for ANSWERING REVIEWERS



January 12th, 2015

Dear Editor,

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

Title: THE SEARCH FOR NAIVE HUMAN PLURIPOTENT STEM CELLS.

Author: Simone Aparecida Siqueira Fonseca, Roberta Montero Costas, Lygia V. Pereira

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 15567

The manuscript has been improved according to the suggestions of reviewers:

Reviewer (1):

“They should mention how to induce selected differentiation pathways in mESCs and hESCs and which main factors are involved.”

WE HAVE INCLUDED THIS INFORMATION IN THE TEXT, REFERENCING A REVIEW ON THE SUBJECT:

In addition, control of induced specific differentiation of mouse ESCs was shown to differ from human ESCs in many cases (reviewed by Scherch et al., 2010), where protocols established with mouse ESCs do not necessarily yield the same differentiated cell population from their human counterpart. This suggests distinct epigenetic states and/or developmental pathways between ESCs from the two species.

“they should mention effects of so called epi-drugs, such as HAT or HDAC inhibitors or others on ESCs pluripotency, proliferation and differentiation.”

WE INCLUDED THIS IN THE CHAPTER OF SMALL MOLECULES:

Nevertheless, small molecules took the spot light in pluripotent stem cell research, including epi-drugs like inhibitors of DNA methyltransferases and histone deacetylases, show to have important roles on cell reprogramming and maintenance of pluripotency (reviewed by David et al, 2011 Looking into the Black Box: Insights into the Mechanisms of Somatic Cell Reprogramming - Genes 2011, 2, 81-106; doi:10.3390/genes2010081).

“Chapter related to iPSCs should be also valuable.”

WE HAVE INCLUDED THE CHAPTER ON iPSCS:

Reviewer (2):

“To be more consistent, the authors should also briefly mention the possible influences of other culture factors, including insoluble factors (substrates or scaffolds) and spatiotemporal variation of soluble factors (nutrients, cell factors, ...).”

WE HAVE FOLLOWED THE SUGGESTION INCLUDING THE FOLLOWING PHRASE IN THE TEXT, AND REFERENCING A REVIEW:

LIF acts on mESC self-renewal mainly by activating Stat3 (signal transducer and activator of transcription 3) through the LIF/Stat3 pathway^[13]. In addition, different matrices and scaffolds are also important for maintenance and/or determination of cell fate (reviewed by Lamshead et al., 2013 - **Defining synthetic surfaces for human pluripotent stem cell culture**. *Cell Regeneration* 2013, **2**:7 doi:10.1186/2045-9769-2-7).

In addition, references and typesetting were corrected.

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

Sincerely yours,



Lygia V. Pereira, Ph.D.

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