Format for ANSWERING REVIEWERS

November 5th, 2013

Dear Editor,
Please find enclosed the edited manuscript in Word format. We thank the reviewers for their thorough and thoughtful review and helpful suggestions.

Title: Brain stem cells as the cell of origin in glioma
Author: Aram S. Modrek, N. Sumru Bayin, Dimitris G. Placantonakis
Name of Journal: *World Journal of Stem Cells*
ESPS Manuscript NO: 6240

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

1. Revision has been made according to the suggestions and comments of the peer-reviewer:

i. This review article by Modrek et al is timely and includes up to date information on what is known about human gliomagenesis. The authors posed interesting questions such as whether cancer stem cells dedifferentiated from differentiated cell types in the tumor? These are questions that are asked by many, yet, remained unanswered. Several approaches have been adopted in an attempt to identify glioma cell of origin. Using the sleeping beauty transposon mutagenesis method, Jenkins and colleague found that the cell of origin for the mesenchymal subtype of GBM is of astroglial-like lineage (Koso et al PNAS 2012; 109), unlike those of the proneural subtype, which is of oligodendrocycte precursor cells lineage shown by Liu C et al (Cell 2011;14:209). This part is lacking in the review.

- We thank the reviewer for bringing the Koso et al PNAS article to our attention. The paper has been included in the review (page 16) and incorporated into the discussion and figure.

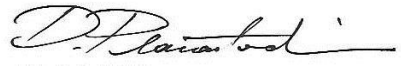
ii. The authors stated that human tumors cannot be used to understand gliomagenesis. Studies have shown that orthotopic glioma derived from glioma stem cells isolated from patient tumor closely resembled de no tumor formation, including the presence of pseudopalisading necrosis and microvascular invasion that are absent from implantation of tumor explants. Please discuss this.

- This is a valid point that was not made clear in our review. We have modified our discussion of the topic to reflect the advantages and disadvantages of using human xenografts to model glioma and gliomagenesis. More specifically, although we agree human tumor xenografts may recreate the human pathology via tumor formation, it does not allow scientists to probe the oncogenic transformation of an endogenous normal brain cell to a glioma. Thus using human tumor xenografts would not allow the identification of the cell of origin, cell of mutation and early cellular events that lead to a glioma. These points are included now within the "Glioma models and the glioma cell of origin" section (pages 12-13).

2. Formatting, grammar and syntax have been corrected.

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

Sincerely yours,



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