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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 65011

Title: Epigenetic modulators for brain cancer stem cells: Implications for anticancer treatment

Reviewer's code: 02446263
Position: Peer Reviewer
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Mexico

Author's Country/Territory: Italy

Manuscript submission date: 2021-03-13

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-03-15 20:53

Reviewer performed review: 2021-03-20 01:48

Review time: 4 Days and 4 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The manuscript by Aballe and Miele reviews the mechanisms of epigenetic modulation and its importance in the biology of brain cancer stem cells (CSCs). The manuscript is well written and provides to the reader basic information as well as cutting edge evidence. However, there are several points that need to be addressed before publication. 1. When listing the characteristics of brain CSCs, author incorrectly state that CSCs have "…the ability to give rise to new tissues (normal or tumoral)". CSCs cannot generate normal tissue since they carry oncogenic mutations. 2. Authors highlight the fact that brain CSC surface markers cannot efficiently discriminate CSCs. Briefly discuss what strategies are better for this purpose and provide references for further reading. 3. Authors have selected some examples to show that epigenetic changes occur in brain CSCs. Please provide details of the studies (not just the conclusion). For example: what methods were employed? how many patients/cell lines were studied? 4. Considering what is mentioned in points 2 and 3 above: are the epigenetic changes the same in CSCs and in tumor bulk cells? If the studies report specific analysis in the CSC pool, were the methods for isolation/characterization adequate? 5. Compare the effects of the drugs in tumor-bulk cells vs. CSCs. For example, you state that HDACi induce cell cycle arrest in CSC, but previously you mentioned that quiescence is a characteristic of CSCs. This comparison is crucial to understand the potential clinical importance of the drugs. 6. In the "Traslational significance…" section, the examples provided require further detail (see comment 3). 7. What are the underlying mechanism of drugs´ toxicity? Are they caused by "on-target" effects? 8. Conclusion needs to be restructured: a) provide your own point of view of how the field is evolving (which should be supported by the evidence presented); and b) you mention that the microenvironment as a key regulator of epigenetics, but the previous text does not elaborate on that. Drugs, although are

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external factors, cannot be considered part of the tumor microenvironment, nor the CSCs´ niche.