

L'Aquila, 9 March, 2021

Dear Editor,

Please find uploaded files containing a revised version of our manuscript, entitled: “Mechanisms involved in selecting and maintaining neuroblastoma cancer cells, and perspectives for therapeutic targeting”, in consideration for publication in the *World Journal of Stem cells*.

We thank the editors and reviewers for the comments made, which have enhanced the quality of this manuscript and answer the specific comments as follows:

We thank reviewer #1 for the comments made and have made the manuscript more concise, as suggested.

We thank reviewer 2 for the comments made, which we have used to improve the manuscript and answer the specific comments as follows:

1. As requested, we have compressed the section “Neural crest”.
2. As requested, we have compressed the section “Neuroblastoma”.
3. As requested, we have re-ordered the “Molecular mechanisms” section to provide a more logical organisation. The new subheading in this section are as follows: Cell surface and membrane-associated molecular protagonists; Growth factors, receptors and signaling pathways; Transcription factors and regulators; Additional molecular protagonists; Additional mechanisms in CSC formation.
4. As requested, we have restructured the section concerning therapeutic aspects, to provide a more logical organisation. The new subheading in this section are as follows: Targeting cell surface markers and membrane-associated molecular protagonists; Inhibiting oncogenes and signaling pathways; Inhibiting transcription factors and regulators; Inhibiting REDOX enzymes; Alternative CSC Inhibitors; Targeting Polyploid Giant Cancer Cells and centrosome amplification; Alternative Approaches; and end with the section “nanoparticles for improving drug delivery and efficacy”.
5. As requested, we have removed lncRNAs from them therapeutic section and added the details to the appropriate section.
6. As requested, we have added a “discussion and conclusion” section, which now includes our own research perspectives, we outline areas that remain to be addressed and add a self-explanatory Figure 5, illustrating NB progression, molecular mechanisms, conditions that promote NB CSC formation (including our own research), conventional NB therapeutic strategies, potential novel therapeutic strategies to improve overall survival in high risk NB and areas to be developed.

Responsabile Segreteria Amministrativo Contabile: Luigi Cavalli – [luigi.cavalli@univaq.it](mailto:luigi.cavalli@univaq.it)

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We thank the Scientific editor for the comments made and answer the specific comments as follows:

1. As requested, we provide a discussion and conclusion section, containing our own research perspectives.
2. We have modified the revised manuscript according to all of the comments made by the reviewers #1 and #2
3. We have kept self-citations within the 10% limit ( $38/481=7.9\%$ )
4. We add the author contribution section, as requested.
5. All figures (5) were prepared by AR Mackay and have been uploaded as pptx files.

Thank you in advance for your consideration and I look forward to your reply

Yours sincerely,



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