

## **Response Letter**

Dear Editor and Reviewer:

Thanks for your letter and for the reviewer's comments concerning our manuscript entitled "*Enhancing the Clinical Translation of Stem Cell Models by Focusing on Standardization and International Regulatory Cooperation*" (ID: 102788). Those comments are all valuable and helpful for revising and improving our paper and the essential guiding significance to our research. We have studied the comments carefully and made a correction that we hope meets with approval. Revised portions are marked in red on the paper. The primary corrections in the paper and the responses to the Reviewer's comments are as follows:

### **Responds to the reviewer's comments:**

#### **Reviewer #1:**

*Scientific Quality: Grade A (Excellent)*

*Language Quality: Grade A (Excellent)*

*Conclusion: Accept*

*Specific Comments to Authors:*

*This paper is a letter to the Editor based on a previously published work. The letter is well written in English and regards the findings of the reference study published by Granjeiro et al. in the World Journal of Stem Cells in 2024, which discussed the role of stem cells in advanced therapy medicinal products (ATMP) for tissue regeneration and drug screening. The authors of the letter focused on what they called two critical aspects that extended beyond the original review: the necessity of international regulatory harmonization and the urgent need for standardized protocols in the development of stem cell-based therapies. The authors reinforced the need to standardize advanced therapy protocols and went further, suggesting this should be done not only by national regulatory agencies but also through international cooperation among international research institutions and regulatory bodies. In summary, the authors concluded that*

*while the original paper by Granjeiro et al. has contributed significantly to understanding the role of stem cell models in ATMP development, they believe that prioritizing international regulatory harmonization and protocol standardization is crucial for realizing the full potential of these therapies. This conclusion is also true, as there are plenty of papers published regarding advanced medicinal therapy products without harmonized protocols, which leads to conflicting results, sometimes with bad results, and turning difficult its use by patients in many countries. In fact, all these actions taken together could not only improve the quality of research performed in this field but also to enhance the efficacy and safety of those procedures. That is why I believe this letter is suitable for publication in the World Journal of Stem Cells. Besides, more studies should be stimulated in order to reinforce this information as well as the publication of papers regarding the regulatory aspects of advanced therapy products worldwide.*

Thank you for your thoughtful and constructive comments on our manuscript "Enhancing the Clinical Translation of Stem Cell Models by Focusing on Standardization and International Regulatory Cooperation". We sincerely appreciate your recognition of the importance of international regulatory harmonization and standardized protocols in advancing stem cell-based therapies.

Your insights align closely with our core argument: the lack of unified global frameworks and standardized protocols leads to fragmented research outcomes. It limits the clinical applicability of advanced therapy medicinal products (ATMPs). We fully agree that addressing these challenges requires national regulatory efforts and active collaboration among international research institutions and regulatory bodies. Your emphasis on the need for more studies and publications focusing on regulatory harmonization further reinforces our call to action.

We are grateful for your endorsement of our letter's suitability for publication in the *World Journal of Stem Cells*. As you highlighted, we hope this work will

stimulate broader discussions and collaborative efforts to improve stem cell therapies' quality, efficacy, and safety worldwide.

Once again, thank you for your time and valuable feedback.

**Reviewer #2:**

*Scientific Quality: Grade B (Very good)*

*Language Quality: Grade B (Very good)*

*Conclusion: Accept*

*Specific Comments to Authors:*

*In the letter, the authors reviewed an article by Granjeiro et al., recently published in the World Journal of Stem Cells, titled "Bioengineering breakthroughs: The impact of stem cell models on advanced therapy medicinal product development". The article explored the critical role that stem cell models play in advanced therapeutic pharmaceutical products (ATMPs), and focused on the need for international regulatory harmonization and the urgent need for standardized protocols in stem cell therapy development. Based on the above, the authors further emphasized the need for standardized stem cell culture and differentiation protocols to enhance the global clinical transformation, safety and consistency of stem cell therapies, focus on these issues makes it a timely and valuable contribution to the ongoing discourse on improving the translational pipeline for stem cell-based treatments, and I think this letter is suitable for publication in the World Journal of Stem Cells. Below are my comments to further improve the article: 1. The authors acknowledge the novelty of the article's focus on the need for international regulatory coordination and the urgent need for standardized protocols in stem cell therapy development. In this regard, the author should put forward his own opinion based on his own professional knowledge, rather than just pointing out its importance in general. 2. As far as I know, there have been some achievements and attempts on the standardization of stem cell culture and differentiation protocols, I suggest the authors take these into account for objective discussion. 3. The format of the manuscript should be modified according to the requirements of the journal, such as citation format, reference format, etc. Overall, this*

*letter is well-suited for publication in the World Journal of Stem Cells due to its thoughtful engagement with the critical topics raised in Granjeiro et al.'s article. By incorporating specific professional insights and actionable recommendations, the authors can significantly strengthen their contribution and provide a roadmap for addressing the challenges associated with the development and clinical application of stem cell therapies.*

Thank you for your thoughtful and constructive comments on our manuscript. We greatly appreciate your recognition of the relevance and timeliness of our work, as well as your valuable suggestions for further improvement.

#### 1. Incorporating Professional Insights and Recommendations:

We sincerely appreciate your suggestion to include more specific professional insights and actionable recommendations. In the revised manuscript, we have expanded our discussion to propose the establishment of a global task force comprising regulatory agencies, research institutions, and industry stakeholders. This task force would develop unified guidelines for stem cell culture, differentiation, and quality control, leveraging existing frameworks such as the International Society for Stem Cell Research (ISSCR) guidelines. We believe this initiative could significantly enhance international collaboration and streamline the development of stem cell therapies.

#### 2. Acknowledging Existing Achievements:

Thank you for pointing out the need to acknowledge existing stem cell protocol standardization achievements. In the revised version, we have included a discussion of recent advancements, such as the alignment of regulatory requirements between the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), as well as the use of Good Manufacturing Practice (GMP)-compliant protocols and artificial intelligence (AI) for optimizing stem cell differentiation. These additions provide a more balanced and objective perspective on the current state of standardization

efforts.

### 3. Format Adjustments:

We have carefully revised the manuscript format to align with the journal's requirements, including citation style, reference formatting, and overall structure. We hope these adjustments meet the journal's standards.

Once again, we sincerely appreciate your thoughtful feedback, which has significantly strengthened our manuscript. We believe these revisions have enhanced our work's clarity, depth, and practical relevance, and we hope the revised version meets your expectations.

We tried our best to improve the manuscript and made some changes. These changes will not influence the content and framework of the paper. Moreover, we did not list all the changes here but marked them in red in the revised paper. We appreciate the Editor and Reviewer's warm work and hope the correction will be approved.

Once again, thanks very much for your comments and suggestions.