

Prof. Lian-Sheng Ma,

Science Editor, Company Editor-in-Chief, Editorial Office

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Dear Lian-Sheng Ma,

Enclosed please find the revised version of our Manuscript N. 65758, entitled “Unveiling the morphogenetic code: a new path at the intersection of physical energies and chemical signaling”, previously submitted to the *World Journal of Stem Cells*.

The revised manuscript has been modified taking into account all the criticisms and suggestions raised by each Reviewer, as detailed below.

Thank you very much for your kind consideration,

Sincerely

Carlo Ventura

Response to Reviewer n. 1

In the paper, there were divided into “three courses” about related studies including evidence, modern tool and new notion. It is a reasonable suggestion for the cellular regulation of bioelectrical signaling. Therefore, this manuscript might be appropriate for its publication after satisfying following minor concerns.

We thank this Reviewer for the appreciation of our work.

1. The authors should describe a “three courses” focusing on stem cell regulation (eg. stem cell maintenance, differentiation, survival et al...) for the purpose of the **WORLD JOURNAL OF STEM CELLS**.

We thank this Reviewer for her/his suggestion. Accordingly the revised version has now been organized incorporating a specific section focusing on the role of bioelectricity in stem cell dynamics, with particular reference to stemness, senescence, paracrine and differentiating pathways. As a result, after the Introduction section, the revised manuscript has been arranged through the following courses:

- **THE PIONEERING STUDIES: EVIDENCE FOR AN ELECTRO-DYNAMIC FIELD IN LIVING ORGANISMS**
- **MODERN TOOLS FOR STUDYING THE BIOELECTRIC SIGNALING IN LIVING CELLS AND TISSUES**
- **BIOELECTRICITY IN STEM CELL DYNAMICS: TUNING STEMNESS, SENESCENCE, PARACRINE AND DIFFERENTIATING PATHWAYS**
- **THE NEW COURSE: ADDING SUPPORT TO THE NOTION OF A MORPHOGENETIC CODE**
- **CONCLUSIONS**

Overall, the revised version presents extensive re-writing and addition of novel information. These changes are highlighted in yellow and traceable throughout the text.

2. It is necessary to mention the role of bioelectricity according to the difference in physical energy.

This issue has been addressed at the end of the Introduction section (page 5, highlighted lines 4-7 from the top), and referenced as well (refs. 1,40).

3. Core tip should be written not to exceed 100 words.

Core tips is now 99 words.

4. In the submission guide for editorial, “Citing more than five references in a single citation, even when separated by a hyphen, should be avoided” is mentioned. Please follow the rules and adjust the citation including the INTRODUCTION section (citation [2-9]).

We have amended the manuscript accordingly: no more than five references are now reported in a single citation.

Response to Reviewer n. 2

In my personal opinion it is a fluently written manuscript which provides important information regarding the role of physical energies and chemical signaling in the morphogenetic code, which consists of the mechanisms and information structures by which networks of cells represent and dynamically regulate the target morphology of the system.

We thank this Reviewer for her/his kind words and appreciation of our study.

1. I suggest developing a figure to summarize the theme proposed in the editorial.

We have now enclosed a Graphical Abstract summarizing the proposed themes and relevant issues discussed in the Editorial.

2. In the following paragraph, “Considering the diffusive properties of such physical stimuli, we may also envision a novel strategy of regenerative medicine relying upon the reprogramming of stem cells in situ, where they are resident in all tissues of the human body.” There are several types of stem cells with different cell potency, in this paragraph the authors are referring to all types of stem cells? I suggest that these concepts are not accurately addressed in the paper and it can make confusion to the readers.

We thank this Reviewer for the suggestion that allows us to better describe the possible implications of our Editorial. The above mentioned paragraph has been moved to the Conclusions section (as it may better be part of the take-home messages). In this section (page 13, highlighted lines 4-16 from the top), we have extensively discussed the diffusive features of physical stimuli within the context of the different types of tissue-resident stem cells, their characteristics, and potency features. These integrations have been referenced, as well (refs. 115,116, and 117-119).

3. I suggest to add the reference that support the following paragraphs:

a. “Bioelectricity is a term coined to identify the ability of electric fields endogenously generated in living cells to afford modulation of biological patterning from the cellular up to the tissue and organ level. In all the cells and tissues, a part of electrically driven signaling originates from ion channels and related ion fluxes. The differential distribution of resting potential across tissues represents an ancestral and conserved modality, highly integrated and connatural with chemical structures, in the establishment of cell signaling networks. Bioelectricity plays a major role in the scaling up dynamics responsible for embryogenesis, and tissue regeneration, while altered non-coherent bioelectrical patterning appears to be involved in the onset of degenerative or malignant states.”

Detailed References have been added to each of the above mentioned paragraphs (page 5, refs. 40,41,42, and 43).

b. “Burr was a fantastic visionary pioneer of studies that only today are creating progressive evidence for the existence of a morphogenetic field and for the need to believe in this potential as an unprecedented chance to access a real comprehensive view on how biological systems acquire coherence. Burr focused on their capability to create dynamically evolving shapes that, while sharing enormous similarities with the simplest microorganisms and our eukaryotic cells, nevertheless entail the evolutionary unfolding not only to complexity, like in multicellular organisms, but to the deeper meaning of biological forms and shapes. This includes the inherent

susceptibility of biological forms and shapes to create further contexts and being then guided by those contexts to orchestrate the coherent morphologies and functions of the entire individual. A fundamental merit of Burr was not only his pioneering work, but his ability to bring science at a subtle line where science itself should find the courage to accompany the scientist to the unrestrainable need of merging with other disciplines, like Arts, Philosophy and Religion, in the effort of accepting other view points to explore the mystery of Life and Universe”.

This paragraph has been referenced (page 7, ref. 61), according to a recently appeared comprehensive review article revisiting Dr. Burr’s pioneering work.

4. Additionally, I would like to congratulate the authors for the editorial and say that I was left with a doubt: can the advent of “omic” technologies contribute in any way to the understanding of the morphogenetic code in the light of chemical signaling and physical energies?

Thank you so much again for this kind consideration of our work! For sure “omic” technologies, and the emerging application of AI strategies to better unveil (stem) cell “decision” strategies, will favor the development of more transdisciplinary efforts among Scientists. In my opinion, we will see consistent paradigm shifts in a relatively near future, having chemical and physical approaches walking hand-to-hand for deciphering the morphogenetic code and understanding how this new knowledge may apply to regenerative and precision medicine.