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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells
ESPS manuscript NO: 15973
Title: The importance of being Nernst: an essential role for synaptogenesis and network emergence as higher-order metrics of neurogenesis in stem cell-derived neuron models
Reviewer's code: 00076088
Reviewer's country: Afghanistan
Science editor: Yue-Li Tian
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

"The importance of being Nernst: an essential role for synaptogenesis and network emergence as higher-order metrics of neurogenesis in stem cell-derived neuron models" by Aaron B Bradford and Patrick M McNutt is a comprehensive overview of the field of stem cell-based in vitro neuronal model systems. The review article focuses on the biological phenomena underlying this approach and the methodological solutions used extensively, including stem-cell biological approaches, reprogramming methodology, differentiation protocols, electrophysiological readouts, optogenetics, immunocytochemistry and in vitro toxicology. The authors' standpoint is that functional synaptogenesis and the development of active neuronal networks are the endpoints of neuronal maturation (neurogenesis) that prove the efficient differentiation of neurons in vitro. Therefore these approaches must be improved to facilitate the functional maturation and network activity of neurons, while measurement of functional activity should be emphasized to unambiguously show these endpoints using various methods. The overview presented in this article is timely, given the increasing number of groups getting involved in pluripotent stem cell-based neuronal differentiation

and in vitro disease modeling. It also enumerates the most critical challenges faced by the field and will be very useful to the readership, especially those researchers who have not been following the development of these methods closely in the last five years. The structure and style of the review allow for easy reading, the list of references provides a useful resource for readers. Below are a few recommendations for consideration of the authors, to better attain the general objectives of the review, and additional questions/reflections that could be included in the article. 1. In general, I understand that keeping in line with the general objectives of a review article, the authors sought to highlight the shortcomings and limitations of many of the currently used approaches and protocols from a theoretical perspective. However, I think that they should also present best practice studies that have already overcome some of these limitations. In this regard, to offer solutions for the above problems, I recommend including a table (or expanding Table 1 of the manuscript) with the studies the authors think should be emphasized to the general readership, including the studies' results and methodological strengths. 2. The abbreviaton mGRASP should be explained. Also in this section (Approaches for morphological and structural characterization of neurogenesis) the differences and the time course of physical and functional synapse formation should be addressed. 3. I agree that miniature excitatory or inhibitory post-synaptic currents are crucial for demonstrating functional synaptogenesis. I would recommend expanding on the time course of the appearance of minis in human pluripotent stem cell derived neuronal populations. After how many days of differentiation should minis be expected in the most important differentiation protocols? 4. The use of calcium imaging and genetically engineered calcium indicators (GECIs) could/should have more emphasis in the article. Although shortly mentioned, these studies may directly demonstrate synaptic coupling and significantly extend electrophysiology data in this regard. Another points possible to mention or discuss: 5. Is there a suggestion for researchers to carry out the investigation of plasticity-related immediate early genes in developing neuronal cultures? What are the possibilities for using paired electrophysiological recordings in culture? Do microfluidic chambers offer an opportunity to this end? 6. Is there any method to accelerate functional synaptogenesis in vitro? Is overexpression of specific transcription factors a feasible option for this method? 7. Are the authors aware of any study successfully using planar multielectro