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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46595

Title: Using induced pluripotent stem cells for modeling Parkinson's disease

Reviewer's code: 03739868

Reviewer's country: Poland

Science editor: Ying Dou

Reviewer accepted review: 2019-03-06 05:55

Reviewer performed review: 2019-03-08 14:34

Review time: 2 Days and 8 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an engaging paper presenting an overview of the potential of human iPSCs to provide a valuable tool for mechanistic study and drug discovery in PD research. The presentation of results is somewhat confusing, as outlined below, and should be addressed before publication of this article. 1. The sentence "The injection of

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6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or the pesticide rotenone into the brain of rats and mice is commonly used in neurotoxin-based in vivo models[30-32]." is only correct with regard to the 6-OHDA-induced PD model. In the other two models, animals are usually injected subcutaneously with rotenone (please refer to reference 32) or intraperitoneally with MPTP (please refer to studies cited in reference 31). 2. Please improve the sentence "Moreover, there are rat strain differences in response to rotenone, suggesting that rotenone may induce atypical parkinsonism from nonselective neuronal death" since the differences in animals' responses to treatments exist not only between different strains but also between labs as well as being due to many factors, such as different protocols of treatment, including doses, frequency, duration, etc., different ages and weights of animals and many others. Of note, the mentioned rat strain differences in response to rotenone are not described precisely or supported by any reference. 3. In Table 1 the in vitro phenotype "Cellular and secreted α-synuclein protein" provided, based on reference 39, should be clarified regarding changes vs. the normal phenotype (increased?) 4. In Table 1 the in vitro phenotype "Increased expression of oxidative stress genes" provided based on reference 52 should be rephrased (oxidative stress-related genes?) In addition in the context of the potential clinical application of patient-derived iPSC-based models of PD, it would be valuable to provide information about 1. sources of the iPSCs and clinical phenotypes in Table 1 2. the use of iPSC-derived glial cells 3. the use of iPSC in the approach of personalized medicine

INITIAL REVIEW OF THE MANUSCRIPT

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[ ] Plagiarism

[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 46595

Title: Using induced pluripotent stem cells for modeling Parkinson's disease

Reviewer's code: 00058340

Reviewer's country: United States

Science editor: Ying Dou

Reviewer accepted review: 2019-03-29 04:10

Reviewer performed review: 2019-03-31 04:26

Review time: 2 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [ ] General [Y] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this review, the authors summarized iPSC-based PD models from patient-specific as well as genome-editing-based iPSCs. They contend that these models may provide extensive insights into pathogenic mechanisms of PD. They acknowledged that despite great advances in gene editing, high off-target risk and low efficacy still make it difficult

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and time-consuming to generate genome-editing-based iPSCs. Thus, improving the efficiency and precision of gene editing is important for generating more isogenic PD-specific iPSCs and control cell lines. Inducing an aged state by long-term culture, overexpression of an aging protein, or small molecules is considered in most iPSC-based age-related PD models. They also acknowledged that iPSCs cannot mimic motor symptoms and some nonmotor symptoms such as depression, agrypnia, hyposmia and impairment of cognition. , 1. The latter statement is a critical point, since PD is a failure of an extensive neural and vascular network connections and interactions, and it is not sure how the change(s) in one cell phenotype will reflect a complex disease such as PD. 2. While the authors extensively reviewed the literature, they did not make a convincing argument how these in vitro models will lead to in vivo translation to the mechanisms and pharmacological interventions.

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[Y] No

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[Y] No