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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 83876

Title: Current overview of induced pluripotent stem cell-based blood-brain barrier-on-a-chip

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03948836
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor, Research Assistant Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Brazil

Manuscript submission date: 2023-02-15

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-03-13 08:05

Reviewer performed review: 2023-03-16 05:21

Review time: 2 Days and 21 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this systematic review, the authors searched published articles that used iPSCs to mimic the BBB and its microenvironment in microfluidic devices. According to the inclusion and exclusion criteria, 14 articles were selected and analyzed in this study. Data extracted from this articles were organized into four topics: (1) Microfluidic devices design and fabrication; (2) Characteristics of the iPSCs used in the BBB model and their differentiation conditions; (3) BBB-on-a-chip reconstruction process; and (4) Applications of BBB microfluidic 3D models using iPSCs. And the result suggested that: (1) Conventional polydimethylsiloxane was the most used material to fabricate in-house chips; (2) IMR90-C4 from human fetal lung fibroblast was the mainly used iPSC cell line; (3) The construction process of the BBB-on-a-chip involved previous coating mostly with fibronectin/collagen IV, followed by cell seeding in single cultures or co-cultures. The manuscript is consistent with the scope of the World Journal of Stem Cells. And this study will be interesting to the readers. However, there are still some questions that need to be addressed. 1. This review aimed to analyze recent literature about BBB models on-a-chip involving iPSCs, and 86% of selected studies have differentiated their

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iPSCs into BMECs. However, like most iPSC-derived cells, BMECs do not fully recapitulate all aspects of their in vivo counterparts. BMECs express some epithelial markers that may not have a purely endothelial cell identity. Thus, whether the articles selected in this review described this question and pointed out the solution or future directions? We hope the authors can discuss this if possible. 2. The permeability of iPSC-derived BBB models is an important factor. We suggest the author list the data of 14 selected articles, if applicable, such as TEER or other evaluation indicators.

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Reviewer's code: 05191118
Position: Peer Reviewer
Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: India

Author's Country/Territory: Brazil

Manuscript submission date: 2023-02-15

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-03-10 01:07

Reviewer performed review: 2023-03-23 19:51

Review time: 13 Days and 18 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [ ] Grade B: Good [Y] Grade C: Fair [ ] Grade D: No creativity or innovation

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Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Reviewer's Comment In this review, the authors have presented an overview of induced pluripotent stem cell (iPSC)-based BBB-on-a-chip. The authors have analysed the literature for BBB models on-a-chip involving iPSCs, described the microdevices, the BBB in vitro construction, and applications. The development of models based on BBB-on-a-chip using iPSCs is promising and is a potential alternative to the use of animals in research. The manuscript is well written and the work is well conducted. The results of different studies are well presented and discussed. The topic is interesting and may be helpful for future studies. I feel this study deserves to be published after addressing the minor points: 1) The authors should thoroughly discuss the challenges of iPSC-based BBB-on-a-chip models, which is missing in the current draft. 2) "Different from primary cells, iPSCs are easily attainable, able to mature into almost any desired cell type. In general, they may be obtained from biopsied tissues or from more accessible sources, such as peripheral blood, renal epithelial cells or dental pulp [3]." The above sentence is not clear and correct. iPSCs cannot be obtained from biopsied tissues or more accessible sources. Please edit it. The revised sentence can be "Different from primary

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cells, iPSCs are easily attainable, able to mature into almost any desired cell type. In general, these can be formed by reprogramming cells obtained tissue biopsy or more accessible sources, such as peripheral blood, renal epithelial cells or dental pulp [3].” The more appropriate reference to cite to these sentences are listed below: https://link.springer.com/article/10.1007/s12015-021-10200-3 https://link.springer.com/chapter/10.1007/5584_2021_660 3) Correct the spelling “disfunction” throughout the manuscript. 4) “paralyze the cells”. “paralyze” word is not appropriate.

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Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Assistant Professor, Surgeon
Reviewer's Country/Territory: China
Author's Country/Territory: Brazil

Manuscript submission date: 2023-02-15

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-03-13 02:27

Reviewer performed review: 2023-03-24 00:37

Review time: 10 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
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Scientific significance of the conclusion in this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

It provides a comprehensive analysis of the literature on microfluidic BBB models involving iPSCs, describing microfluidic devices, BBB in vitro constructs and applications. The review is well written and the results are presented in a clear and concise manner. However, there are some issues that need to be improved before publication. First, the introduction should provide more background knowledge about the blood-brain barrier. Describe how the current iPSC-based BBB-on-a-chip can overcome the limitations of traditional in vitro models and possible future directions. Second, the methods section should be more detailed. Please write in detail the literature search keywords, inclusion and exclusion criteria, search strategy and data extraction details. Third, in the section "Microfluidic devices design and fabrication", in addition to an overview of the materials and specifications used in the literature, these design differences should be discussed, what their advantages and disadvantages are, and which aspects of the BBB model evaluation are more important. Fourth, please add learning related to iPSC culture and differentiation induction. In general, mTeSR1 and Essential Medium 8 culture systems are both widely used iPSC culture systems, but

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these media are not involved in the differentiation process. This paper should focus on summarizing the media used in the differentiation of iPSC cells called BBB process. Also, why was doxycycline used in Middelkamp's study? This is a reagent that is not normally required in cell culture, please explain. Fifth, in the section "Applications of BBB microfluidic 3D models using iPSCs", you mentioned "Neuronal functionality", why do neurons appear in the BBB microfluidic system? Why do neurons appear in BBB microfluidic systems? Please elaborate. Finally, please add the prospect of iPSC-based BBB-on-a-chip development, i.e., what are the current challenges that need to be addressed and what are the foreseeable potential impacts of this model in drug screening or medical research. Overall, this study provides valuable insights into the use of iPSCs to construct BBB models. However, the manuscript could benefit from some revisions and more detailed information to improve its clarity and impact.