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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 96782

Title: ATP-Binding Pocket Inhibitor for Mixed Lineage Kinase Domain-like Protein (MLKL) Attenuated Alcoholic Liver Disease via Necroptosis-independent Pathway

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05917261
Position: Peer Reviewer
Academic degree: Md

Professional title: Dcotor

Reviewer's Country/Territory: China

Author's Country/Territory: South Korea

Manuscript submission date: 2024-05-15

Reviewer chosen by: Hong-Xin Jiang

Reviewer accepted review: 2024-07-15 07:31

Reviewer performed review: 2024-07-26 07:04

Review time: 10 Days and 23 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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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) [ ] Minor revision [Y] 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 the present study, the authors investigate the possibility of inhibition of the ATP-binding pocket of MLKL for the treatment of necroptosis-associated liver diseases. To confirm the hypotheses, cell death analysis following necroptosis stimuli was evaluated using cell proliferation assays, flow cytometry, and electron microscopy in various cells including HT29, RAW264.7, U937, and LX-2 cells. Both alcoholic and non-alcoholic fatty liver disease animal models were used to determine the possibility that MLKL ATP pocket inhibitors could attenuate liver injury. In addition, the human liver organoid system was also used to evaluate the potency to attenuate inflammation with the MLKL ATP pocket-binding inhibitor. The introduction is well written and provides a clear background on the topic. The methodology is sound and the experimental design is appropriate for the research question. The results are presented clearly and are supported by appropriate statistical analysis. The discussion is insightful and provides a good interpretation of the results, but lacks a critical evaluation of the study's findings in the context of existing literature. The references are relevant and up-to-date. However, the author could benefit from providing a more detailed literature

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review to demonstrate the novelty of the study. The manuscript is generally well written, but there are a few instances of awkward phrasing and grammatical errors. A thorough proofreading would improve the overall quality of the paper. Overall, the manuscript is well written and presents interesting findings, which may present a valuable contribution to the field. Besides, the manuscript is rich in data but a few issues need to be addressed. 1. Where is the MLKL ATP-binding inhibitor from and what are the differences among Compound-4, CPD4, and CPD30? 2. Why are HT29 (human colon cancer cells), RAW264.7, U937 cells (human monocytes), and LX-2 (Human hepatic stellate cells) cells used here? What's the relationship between these cells and necroptosis-associated liver diseases? 3. Statistical analysis should be performed for all results. For example, there is no statistical analysis for some results in Figure 1D. 4. "Figure 4. MLKL ATP-binding inhibitor cannot evade cell death after necroptosis stimuli but increase inflammation." Here should be inhibition of inflammation. 5. When describing the results of Figure 4A-4D, the type of cells involved should be specified. 6. "Data Availability A data availability statement is compulsory for all research articles. This statement describes whether and how others can access the data supporting the findings of the paper, including 1) what the nature of the data is, 2) where the data can be accessed, and 3) any restrictions on data access and why. If data are in an archive, include the accession number or a placeholder for it. Also include any materials that must be obtained through a Material Transfer Agreements (MTA)." There is no substantial content in this section. 7. Some sentences should be modified to be more clarified. E.g., "At the same time MLKL also involved cell death pathway as well as cell activation via NFkB-mediated inflammatory pathway at the same time, and it depends on the type of cell and situations.", "Recent studies have suggested many various alternative pathways of MLKL.".

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Peer-review model: Single blind

Reviewer's code: 07756729
Position: Peer Reviewer
Academic degree: Md

Professional title: Doctor

Reviewer's Country/Territory: Ghana

Author's Country/Territory: South Korea

Manuscript submission date: 2024-05-15

Reviewer chosen by: Shang Wu

Reviewer accepted review: 2024-09-30 09:27

Reviewer performed review: 2024-10-02 11:28

Review time: 2 Days and 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] 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

A search in one database indicated that the short title so presented had been published already… find below: https://www.sciencedirect.com/science/article/pii/S0300483X24001458#:~:text=Mlkl%20deficiency%20can%20alleviate%20acute,NF%2D%CE%BAB%20p65's%20nuclear%20entry. Thus, it is important for authors to bring out the novelty in their research. Authors said nothing on data availability. Find below statements provided by the authors that actually did not indicate data availability: Data Availability A data availability statement is compulsory for all research articles. This statement describes whether and how others can access the data supporting the findings of the paper, including 1) what the nature of the data is, 2) where the data can be accessed, and 3) any restrictions on data access and why. If data are in an archive, include the accession number or a placeholder for it. Also include any materials that must be obtained through a Material Transfer Agreements (MTA). Abstract: Well noted… but what is the gap the authors are addressing since there seem to be other published articles Introduction: Stating hypothesis and refencing it as such makes readers wonder if the working hypothesis is actually an original hypothesis

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from the others or a borrowed hypothesis from other published work. See below: "So, our hypothesis is whether ATP pocket inhibitor can regulate inflammation via necroptosis independent pathway.2 In this study, we investigated the role of the ATP-binding pocket of MLKL as a possible novel target of MLKL." Method: Just wondering why I still cannot locate ethical clearance statement; study design; were archival samples used or... What is CDHFD? Find below: 'Animal models of non-alcoholic fatty liver disease were fed a CDHFD for six weeks.' Results: What is 5AD? See below: 'We initially conducted a toxicity test using 5AD, a methylation inhibitor, based on a study indicating that hepatocyte hypermethylation does not induce necroptosis. Results showed that 5AD exhibited no significant cytotoxicity, even at 10 μM, compared to the untreated group' Discussion: Start discussion with main finding rather. Conclusion: I could not locate the conclusion in the main text after discussion. Authors should kindly rectify this.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 96782

Title: ATP-Binding Pocket Inhibitor for Mixed Lineage Kinase Domain-like Protein (MLKL) Attenuated Alcoholic Liver Disease via Necroptosis-independent Pathway

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05917261
Position: Peer Reviewer
Academic degree: Md

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: South Korea

Manuscript submission date: 2024-05-15

Reviewer chosen by: Ming Fan

Reviewer accepted review: 2024-10-28 11:17

Reviewer performed review: 2024-10-30 02:44

Review time: 1 Day and 15 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) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

All my concerns have been addressed, and I have no further questions.