



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 101528

Title: Hepatocellular carcinoma resistance to Tyrosine Kinase Inhibitors: current status and perspectives

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04505255

Position: Peer Reviewer

Academic degree: Chief Physician, MD, Postdoctoral Fellow

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2024-09-18

Reviewer chosen by: Shang Wu

Reviewer accepted review: 2024-11-28 01:30

Reviewer performed review: 2024-12-01 06:05

Review time: 3 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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

SPECIFIC COMMENTS TO AUTHORS

This manuscript explores the critical issue of tyrosine kinase inhibitor (TKI) resistance in hepatocellular carcinoma (HCC), focusing on the role of ARHGAP12 as a potential therapeutic target. The authors discuss the underlying mechanisms of TKI resistance, such as signaling pathway reactivation, tumor microenvironment influences, and drug efflux pump activity, and highlight the involvement of ARHGAP12 in focal adhesion (FA) pathways. Through a combination of bioinformatics analyses and prior literature, the manuscript provides a theoretical framework for targeting ARHGAP12 in overcoming drug resistance. Additionally, the authors explore potential combination therapies involving TKIs, immunotherapy, and traditional Chinese medicine, which enhances the clinical relevance of the discussion. The manuscript addresses a highly relevant and clinically significant issue, as TKI resistance remains a major obstacle in the management of advanced HCC. The focus on ARHGAP12 is novel and supported by evidence from transcriptomic and protein-level analyses. Furthermore, the authors' discussion of combination therapies, particularly the integration of immune checkpoint inhibitors and traditional Chinese medicine, provides actionable insights that could



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guide future therapeutic strategies. The writing is generally clear and structured, and the topic aligns well with the scope of the journal. While the manuscript is informative, it requires minor modifications to strengthen its impact. First, the figures and tables could be improved for clarity and comprehensiveness. For example, Figure 1 would benefit from higher resolution and more detailed annotations, while Table 1 should include additional information about the clinical outcomes or trial statuses of the listed therapies. Finally, minor language revisions are needed to address grammatical inconsistencies and improve readability. Phrases such as "ARHGAP12 may influence FA by regulating ITGB1" are somewhat repetitive and could be rephrased for clarity. Besides, don't use abbreviations for keywords. Each keyword should be separated by semicolons, and do not use "and" to connect them. Overall, this manuscript presents a novel perspective on HCC treatment and provides valuable insights into overcoming TKI resistance. With minor revisions to improve data presentation, language, and depth of discussion, it will be suitable for publication.



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Peer-review model: Single blind

Reviewer's code: 08294280

Position: Peer Reviewer

Academic degree: Chief Physician, MD

Professional title: Doctor

Reviewer's Country/Territory: India

Author's Country/Territory: China

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Reviewer chosen by: Shang Wu

Reviewer accepted review: 2024-11-29 07:48

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Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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

SPECIFIC COMMENTS TO AUTHORS

Myself Dr Utpal Gaikwad, have gone through the draft of Letter to editor and very please to inform all authors that they did remarkable job in precise assessment of the published article by Wang et al in World journal of Gastrointestinal Oncology which investigated the expression of Rho-gtpase activating protein 12 (ARHGAP12) in hepatocellular carcinoma (HCC) and its relationship with resistance to tyrosine kinase inhibitors (TKIs). As we all know, tyrosine kinase inhibitors (TKIs) despite the significant clinical efficacy in treating hepatocellular carcinoma (HCC), the issue of resistance which is quite common; requires further research and resolution. Future studies first understand pathways of resistance generation to tyrosine kinase inhibitors and should explore combination therapies, optimize treatment regimens, and identify new targets to overcome resistance to tyrosine kinase inhibitors so as to improve treatment outcomes and quality of life for hepato-cellular carcinoma (HCC) patients. In this regard assessing ARHGAP12 in hepato-cellular carcinoma (HCC) and its role in resistance to tyrosine kinase inhibitors (TKIs) can be a practice changing, for better stratification of patients and personalizing their treatment so as to improve therapeutic ration. This Letter to



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Editor is very well formulated and I must praise authors for the same. I want to add few minor suggestions which are as follows, many of which are with regards to grammar, rephrasing of few sentences and references; which might help to make this article slightly better. Kindly go through the following suggestions which are highlighted in the file for better understanding 1. Line 70-71 - Sentence re-phrased 2. Line 76 - Sentence re-phrased 3. Line 79 - Grammatical correction 4. Line 80 - key word added 5. Line 115 - Kindly add appropriate reference 6. Line 116 - Kindly add appropriate reference 7. Line 142 - Kindly add appropriate reference 8. Line 153 - Grammatical correction 9. Line 154 - Grammatical correction 10. Line 160 - Kindly add appropriate reference 11. Line 202 - Grammatical correction I hope these inputs were valuable and my best wishes to Authors for this and future projects.



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Title: Hepatocellular carcinoma resistance to Tyrosine Kinase Inhibitors: current status and perspectives

Provenance and peer review: Invited Manuscript; Externally peer reviewed

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Reviewer's code: 08385864

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Academic degree: Associate Professor

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

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Reviewer chosen by: Huo Liu

Reviewer accepted review: 2024-12-06 06:34

Reviewer performed review: 2024-12-16 02:05

Review time: 9 Days and 19 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input checked="" type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input checked="" type="checkbox"/> Grade D: No creativity or innovation



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

SPECIFIC COMMENTS TO AUTHORS

Miao et al discussed the current status and prospect of drug resistance to targeted therapy in HCC via commenting on the recent published article (arhgap12 regulated FA to promote TKI resistance in HCC). Overall, the manuscript was poorly organized with no novelty. Currently, most patients with HCC are treated with immune checkpoint inhibitors (ICIs) based combination therapy with bevacizumab or TKIs. Resistance to these combination therapies were the concerned research focus. In the introduction and current situation and challenges of tki resistance section, the description was out of date. The authors should be more careful about their manuscript, ARHGAP12 regulated FA pathway, FA stands for focal adhesion or Fanconi anemia? The mechanism summarized in Figure 1 and advances in hcc drug combination in table 1 was not comprehensive and out of date. The authors should refer to recent important clinical trials and reviews. The combination of PD-1 and Lenvatinib (RCT:LEAP-002), PD-L1 with bevacizumab (RCT: IMBRAVE 150), PD-1 with Cabozantinib et al should be listed in table 1. The action mechanism listed in table 1 should be more concised. Vessel co-option was an important mechanism of TKI resistance in HCC. The tile was improper, it could be changed to



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Resistance to tyrosine kinase inhibitors in hepatocellular carcinoma: current status and prospects The quality of the language was very poor and should be revised intensively: "target direction" "Understanding the molecular mechanisms of hepatocellular carcinoma, with particular reference to TKI resistance." "was found and combined with tyrosine kinase inhibitors" "a new target direction" "TKIs drug use data" "protein immunohistochemistry level" "SCNA-SEQ" "clinical TKI resistance" "These inhibitors interfere with tumor blood supply and cell proliferation, thereby reducing tumor angiogenesis and directly inhibiting tumor cell proliferation," the two sentences are the same thing. "evading TKI effects" "Immunotherapy drug combination" "malignant hepatocytes" are still hepatocytes, should it be malignant hepatoma cells? "ARHGAP12 may play a critical role in the development of resistance to HCC." resistance to HCC?



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04505255

Position: Peer Reviewer

Academic degree: Chief Physician, MD, Postdoctoral Fellow

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

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Reviewer chosen by: Meng-Liu Luo

Reviewer accepted review: 2025-01-02 05:21

Reviewer performed review: 2025-01-02 08:50

Review time: 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors should carefully consider and address each comment from the reviewers and respond to them point by point. The authors should revise the manuscript thoroughly based on my review comments. Additionally, the authors should comprehensively revise the manuscript according to the previous reviewers' comments.

General Comments: The manuscript addresses a highly relevant and pressing issue in the field of hepatocellular carcinoma (HCC) treatment—resistance to tyrosine kinase inhibitors (TKIs). The focus on ARHGAP12 as a potential molecular target is innovative, and the authors make a compelling case for its clinical significance. However, there are areas that require improvement for clarity, depth, and methodological rigor.

Specific Comments: Abstract: The abstract should explicitly mention the methodologies used (e.g., sequencing techniques, database analysis) to give readers a complete overview of the study. Introduction: While the background on HCC and TKI resistance is thorough, the introduction lacks a strong transition to ARHGAP12 as the focal point. A brief mention of its biological relevance earlier in this section would be beneficial. Figures and Tables: Figure 1 (Mechanism of Drug Resistance) lacks clarity in some labels and connections. Consider revising for better readability. Table 1 includes excessive detail on



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drug combinations unrelated to the manuscript's central theme. A concise summary would suffice. **Methods:** Provide more detail about the bioinformatics tools and statistical methods used for gene expression and protein interaction analyses. Clarify the selection criteria for databases and datasets. **Discussion:** The discussion is comprehensive but occasionally digresses into general topics unrelated to ARHGAP12. Focus on how the findings inform clinical strategies against TKI resistance. **Conclusion:** A stronger conclusion emphasizing ARHGAP12's potential as a therapeutic target, supported by actionable recommendations for future research, would enhance the manuscript's impact. **References:** Ensure the reference style adheres to the journal's guidelines. Some references are overly detailed.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Position: Peer Reviewer

Academic degree: Chief Physician, MD

Professional title: Doctor

Reviewer's Country/Territory: India

Author's Country/Territory: China

Manuscript submission date: 2024-09-18

Reviewer chosen by: Meng-Liu Luo

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Reviewer performed review: 2025-01-02 10:25

Review time: 1 Hour

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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Scientific significance of the conclusion in this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

All suggestions/ modifications are well incorporated by authors so I do not have any modifications/ suggestions.