Peer-review

Gupta, Iraa, and Nina Krause. 2025. “Immune Evasion Strategies of Mycobacterium Tuberculosis.” *Journal of High School Science* 9 (2): 44–69.

This manuscript is significantly short on content, analysis, depth, erudition and organization and cannot be accepted as a review. The manuscript must be organized per the title, i.e. present each invation/evasion strategy including mechanisms with references. Then present and explain how these mechanisms are targetable by drugs with examples and references. See below:
1. invasion strategy 1: inhibiting lysosome-phagosome fusion , then present and explain mechanims by which the pathogen achieves this (including KO/KI models). Then present and explain how these mechanims may be targeted by drugs. each step should have examples and references. The references for drug development in this step should include: https://doi.org/10.1016/j.intimp.2023.109696, https://doi.org/10.3389/fimmu.2023.1227467, https://doi.org/10.1186/s13578-023-01107-2, https://doi.org/10.3390/biom13060968, https://doi.org/10.1101/2023.10.01.560397, https://doi.org/10.1111/sji.13261, https://doi.org/10.1074/jbc.ra120.012809, https://doi.org/10.1093/femspd/ftac004, https://repositorio.butantan.gov.br/bitstream/butantan/4805/1/Repurposing Tamoxifen as Potential Host-Directed Therapeutic for Tuberculosis.pdf, https://doi.org/10.1146/annurev-micro-041020-025803, https://doi.org/10.3390/cells12060828
This needs to be done for each invasion/evasion strategy. An exhaustive search of the literature needs to be performed including any drugs in clinical trials (and even preclinical trials). search clinicaltrials.gov. In summary, this manuscript needs signficant revision, expansion, organization, depth, erudition and analysis before it can be considered for another round of review.

Unveiling the Evasion Strategies of Mycobacterium Tuberculosis: Insights into Three Key Strategies

Addressing the Reviewer’s Comments

I have taken the feedback given by the reviewer into careful consideration and have made the following changes.

Instead of discussing 4 evasion strategies and their treatments separately, I have decided to only focus on 3 evasion strategies go into great depth of each of them. For example, I have gone into more detailed about the evasion strategy itself while also using Knock in and knock out models as the reviewer had suggested.

Additionally, instead of discussing the treatments in a different section, I have now included specific treatments which can target each specific strategy, adding more detail and depth into each paragraph, something which my first draft lacked, as mentioned by the reviewer. The information about the treatments involve the discussion of specific drugs that have been used in the past in addition to drugs that are currently being tested that may be beneficial.

I have also gone ahead and restructured the paper to make it more cohesive and ensure it has a better flow of information. While the introduction and the section about the immune system stays the same, I have shifted the section about the symptoms and its impact on human well-being to the beginning of the paper.

Furthermore, the sections about existing treatments, discussion and the conclusion are more or less the same.

The following comments and content from my last review have not been incorporated into the manuscript. Please check and include in the manuscript along with suitable explanation, discussion and references.
https://doi.org/10.1016/j.intimp.2023.109696
https://doi.org/10.3389/fimmu.2023.1227467, section 4, "…….the development strategy of organelle drug discovery rather than the framework of disease-by-disease drug discovery……"
https://doi.org/10.1186/s13578-023-01107-2, Mitophagy and Bnip3
https://doi.org/10.1074/jbc.RA120.012809, SL-1 MTorC1
https://repositorio.butantan.gov.br/bitstream/butantan/4805/1/Repurposing Tamoxifen as Potential Host-Directed Therapeutic for Tuberculosis.pdf
https://doi.org/10.1146/annurev-micro-041020-025803, ubiquitin
https://doi.org/10.3390/cells12060828, DRAM1
2.The Journal's expectations for a review manuscript can be found at https://jhss.scholasticahq.com/about. "….Publication of a review paper in the Journal of High School Science differentiates students who are meticulous, thoughtful and knowledgeable from those who can **additionally** connect disparate concepts in a coherent way, think and/or speculate about the problem differently than has been done before and pose implementable solutions. This means that you will need to present at least one new way of thinking about how to circumvent the evasion strategies of MTB. I have directed you to one very interesting way below. (you are free to think and present your own). This is a requirement for publication.
Half the world's population is estimated to carry latent MTB. It is therefore necessary to report mechanisms that may be used to eradicate latent MTB; especially since latent MTB can be reactivated in the presence of a viral infection. If that viral infection is a pandemic (like Covid19), there could be billions of people in whom the MTB is reactivated. Please read the following (and numerous related) manuscripts for an interesting way to circumvent latent MTB. This is ongoing research.
https://doi.org/10.3389%2Ffimmu.2021.695278
https://doi.org/10.3389/fimmu.2020.594572
https://doi.org/10.1101/2020.11.14.382572
3.Please revise your References section. As currently presented, it is not formatted to Journal guidelines. A live link must be included as part of every reference. Do not use the software's automatic numbering algorithm to number references; instead do this manually. Presentation of every reference must be consistent. More than 6 authors, must list 6 authors followed by et al., Please see the website for proper formatting requirement for references.
4.You will need an "Abbreviations" section before the "References" section. Please make sure that all the abbreviations used in the manuscript are presented in their full names/form in this section.

Unveiling the Evasion Strategies of Mycobacterium Tuberculosis: Insights into Three Key Strategies

Addressing the Reviewer's Comments

I have taken the feedback given by the reviewer into careful consideration and have made the following changes.

1. I have integrated relevant information from each of the sources the reviewer has kindly provided to me. Majority of this information is in the sections 'The Evasion Strategies', 'A) Inhibition of Phagosome and Lysosome fusion' and the 'Discussion'

2. The 'Discussion' section now also discusses the views regarding the use of stem cells as a possible treatment. This is a unique and interesting way in which I think M. tuberculosis infections can be reduced and treated. All of the mentioned sources have been reviewed and integrated into the paper.

3. All references contain live links and is consistent in formatting. Number of authors has been kept in mind. Furthermore, I have followed the following citation format as mentioned on the JHSS website: *"Davies NM, Jamali F. COX-2 selective inhibitors cardiac toxicity: Getting to the heart of the matter. J Pharm Sci, 7: 332-336, 2004."*

4. 'Abbreviations' section is added before 'References' Section as suggested by the reviewer.

Thank you!

You have not addressed all my prior comments. I did not see the keywords DRAM1, tamoxifen…. neither did I see that the novel method of spreading herd immunity by ESAT-6 containing EV aerosols was addressed adequately. https://doi.org/10.1101/2020.11.14.382572
In addition, the paradigm of organelle drug delivery and a deeper explanation of Ubiquitin involvement was missing from the resubmitted manuscript.
When you have adequately addressed all my comments and submitted a word document of the manuscript, I will be happy to review again.
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https://doi.org/10.3389/fimmu.2023.1227467, section 4, "…….the development strategy of organelle drug discovery rather than the framework of disease-by-disease drug discovery……"
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The Journal's expectations for a review manuscript can be found at https://jhss.scholasticahq.com/about. "….Publication of a review paper in the Journal of High School Science differentiates students who are meticulous, thoughtful and knowledgeable from those who can additionally connect disparate concepts in a coherent way, think and/or speculate about the problem differently than has been done before and pose implementable solutions. This means that you will need to present at least one new way of thinking about how to circumvent the evasion strategies of MTB. I have directed you to one very interesting way below. (you are free to think and present your own). This is a requirement for publication.

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Please revise your References section. As currently presented, it is not formatted to Journal guidelines. A live link must be included as part of every reference. Do not use the software's automatic numbering algorithm to number references; instead do this manually. Presentation of every reference must be consistent. More than 6 authors, must list 6 authors followed by et al., Please see the website for proper formatting requirement for references.
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Unveiling the Evasion Strategies of Mycobacterium Tuberculosis: Insights into Three Key Strategies

Addressing the Reviewer's Comments

I have taken the feedback given by the reviewer into careful consideration and have made the following changes.

1. As suggested, I have included keywords such as DRAM1 and Tamoxifen in addition to relevant information about these keywords. This is in section 'The Evasion Strategies, A: Inhibition of Phagosome and Lysosome fusion'
2. I have added to the 'Discussion' section by adding information about Organelle Drug Delivery and Ubiquitin's Involvement in Host-Pathogen interactions.
3. I have added the new abbreviations to the 'Abbreviations Section'
4. I have included the *live* 'doi' or website links in each citation and have made the formatting consistent.

Thank you!

Thank you for addressing my previous comments. Accepted but will require extensive copyediting.